IMMUNITY

Innate (natural) immunity

1st line of defense

Acquired (Adaptive) immunity

2nd line of defense : B &T lymphocytes

Components of innate immunity

- Mechanical &chemical barriers
- Normal bacterial flora
- Circulating effector proteins
- Phagocytosis
- Direct EC killing

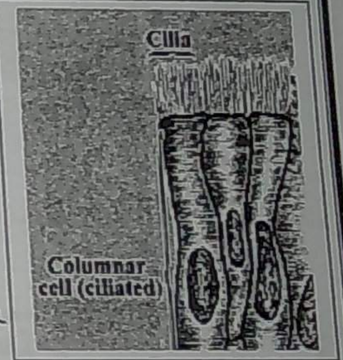
I-Mechanical & Chemical barriers

A-Mechanical barriers

Intact skin & epithelial surfaces
Prevent entry of organisms

Sticky mucus covering RT mucosa
Trap org.

Epithelial cilia
Sweep inhaled org.



B-Chemical barriers

Microbicidal factors in BFs

ALD 23da2 el bactria

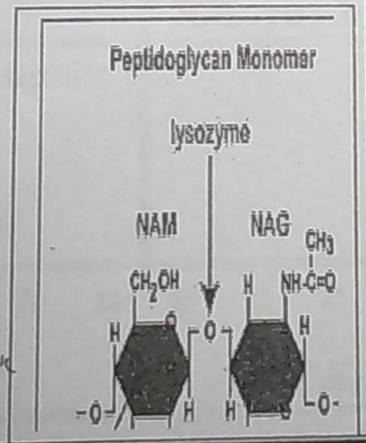
Acids

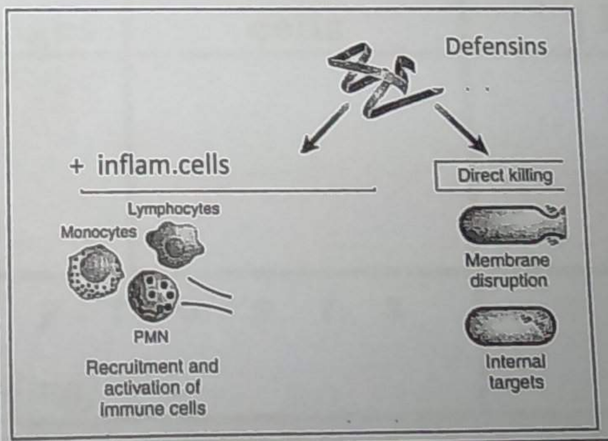
- ***Lactic & fatty acids*** in sweat& sebaceous secretions (skin)
- ***In gastric juice***

Lysosymes

In tears, saliva & nasal secretions

Destroy peptidoglycan → osmotic rupture





Defensins

- Secreted by epithelia & some WBCs
- ♥ Toxic to org. ♥⊕ inflam. cells

♥ destroy the membrane of organism

II - Normal bacterial flora

⊖ growth of pathogenic bacteria & fungi by

Competition for limited attachment sites on host cells

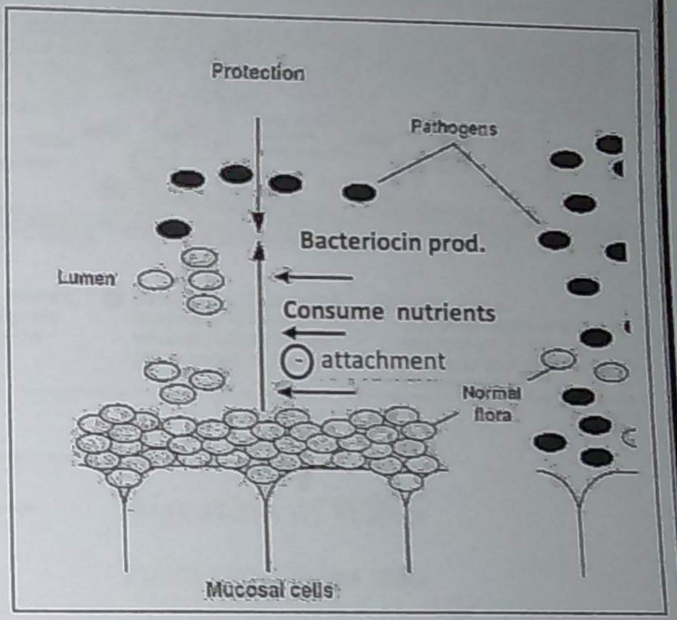
Established normal flora aren't displaced by incoming microbes

Competition for essential nutrients

→ Flora are already adapted "متعوده حاليًا"

Production of bacteriocins

Bacterial products that kill or ⊖ strains of same or closely related species



Cells of innate immunity

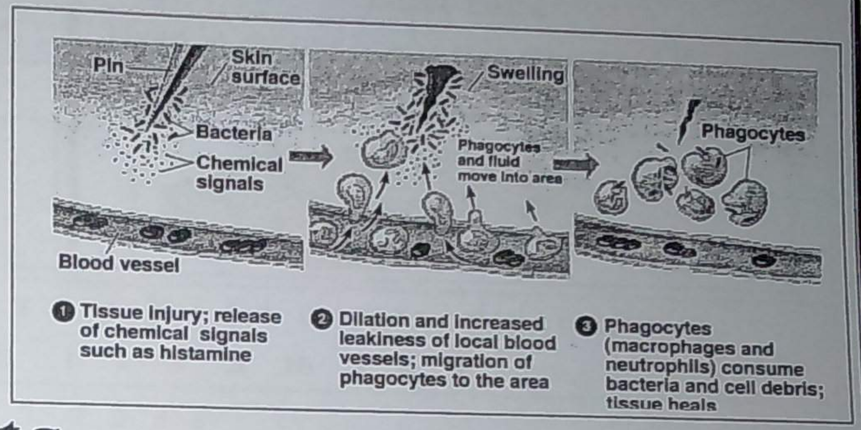
Granulocytes			Monocytes & Macrophages	Dendritic cells	Natural killer cells (non-phagocytic cells) (lymphocytes)
Eosinophils (non-professional)	Basophils & Mast cells	Neutrophils			
EC killing		*Phagocytosis (IC Killing)*			EC killing (cytotoxicity)
Inflammation in mucosa					

Inflammation

Definition

Process during which cells of IS & their active products

are concentrated at the site of infection or tissue damage



Aim

Eradication of infectious agents

Events

VD ---→ **↑ Capillary permeability** ---→ **Migration of WBCs**

↑ local blood supply to the site of infection

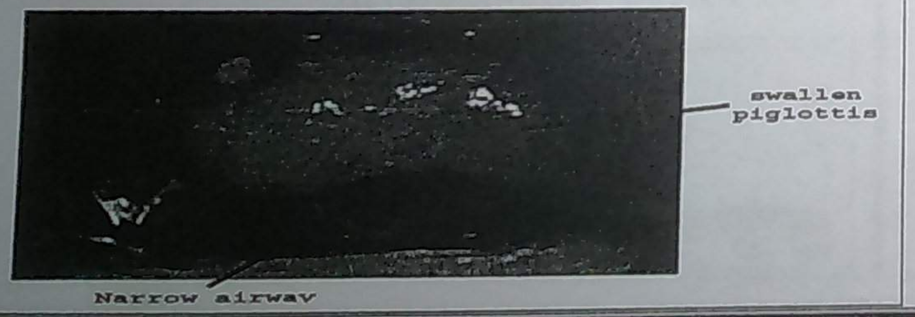
Intitation of immune response

From capilleries into affected tissues

Harmful effects

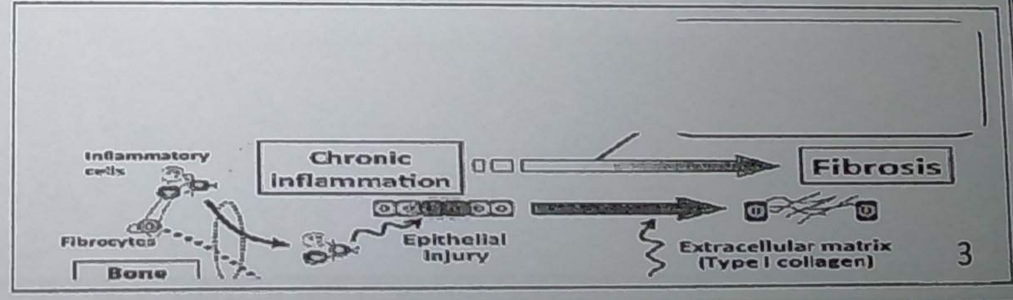
Mechanical obstruction of airways

By swollen epiglottis → acute epiglottitis

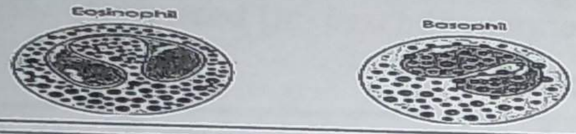
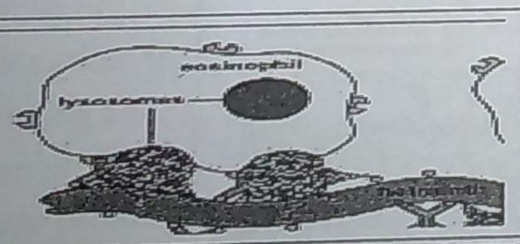


Scarring & Loss of functions

By tissue damage due to chronic inflam.



Important inflammatory cells

	Eosinophils	Basophils	Mast cells
1-Site	**Blood** ⟶ recruited out to tissues (when needed)		**Fixed in tissues :** under skin, mucosa of RT&GIT
2-Structure	**i.Bilobed** nucleus 		**i.Round** nucleus 
	ii.Acidophilic granules containing: ♫ Basic protein	**ii. Basophilic granules containing :** ♫ Histamine	
	♪ *Peroxidase* ♪ *Hydrolase*		
3-Functions	***i. Inflammation in mucosa*** ***ii. Allergy*** 		
	iii. Damaging parasites 		

III - Circulating effector proteins

A - Complement System

Group of soluble plasma proteins **(C1-C9)** circulating in **inactive** form

⬇

Activated (in cascade manner) ***by microbial surfaces (Ags)***

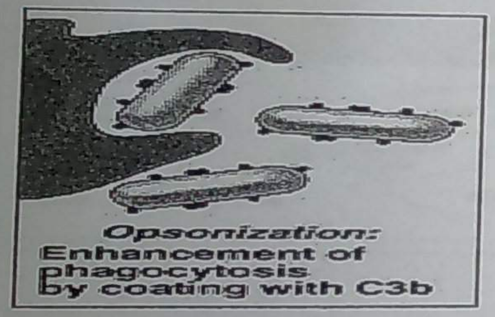
Functions

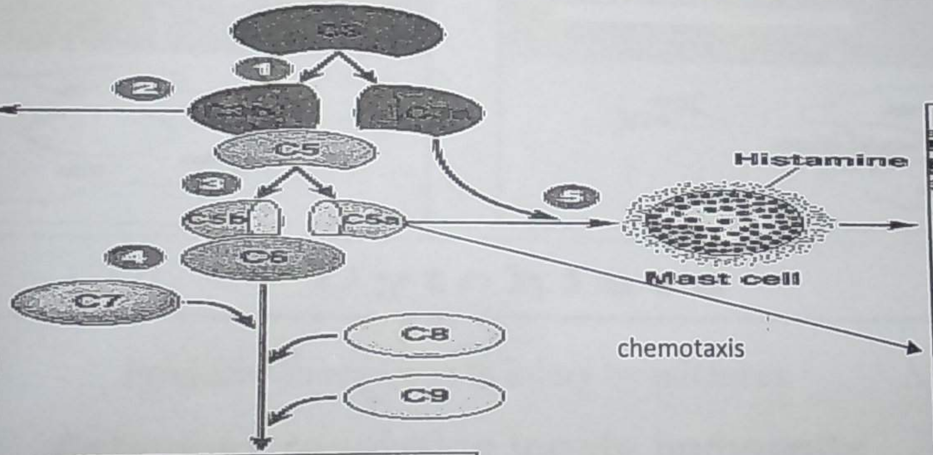
Direct lysis of bacteria **(C5b6789)**

Enhance phagocytosis **(C3b is opsonin)**

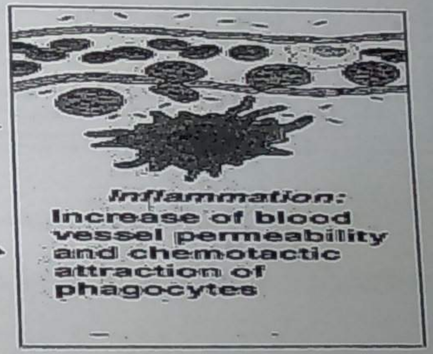
Degranulation of mast cells & basophils (C3a&C5a) ⬇ ↑ vascular permeability & recruitment of phag.cells (VD)

Chemotaxis (C5a)



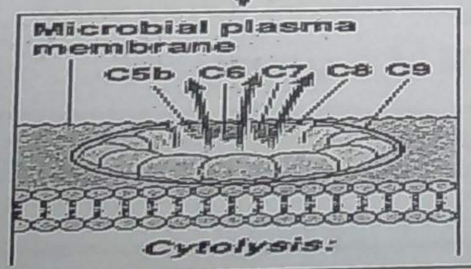


Degranulation & Chemotaxis



Opsonization

A process in which an org. is rendered more susceptible to phagocytosis by coating an opsonin (blood serum protein) e.g C3b,Ab,acute phase protein



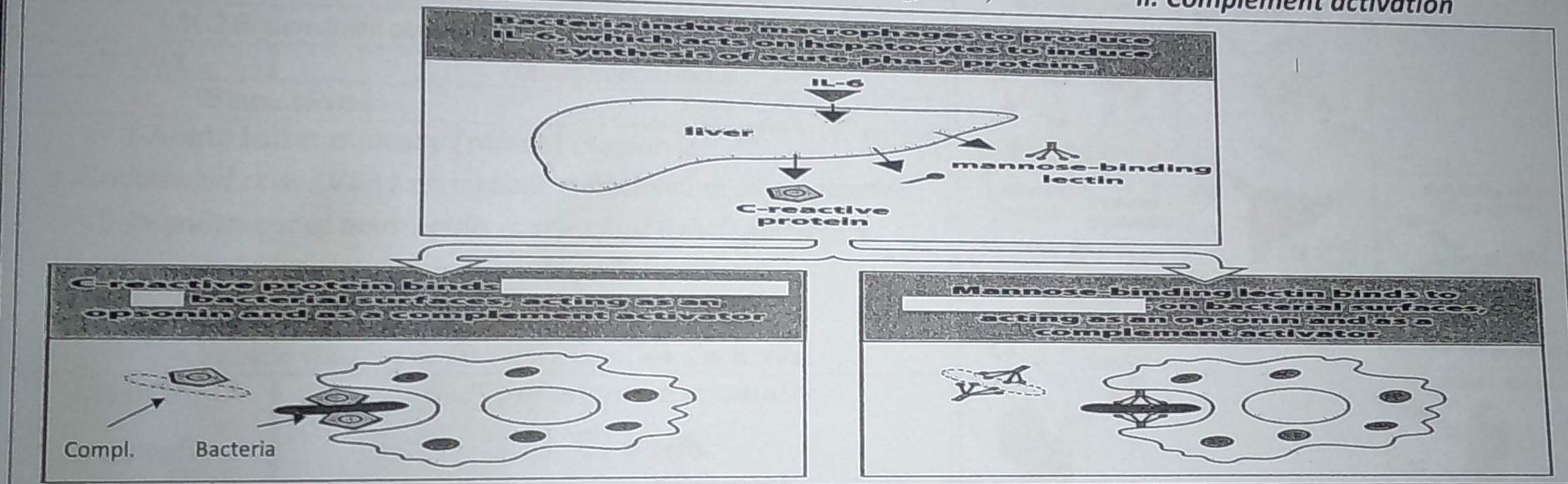
Direct bacterial lysis

B-Acute phase proteins

Release
From liver
under effect of *TNFα,IL1&6*

Examples
- C-reactive protein
- Mannose binding protein (lectin)

Functions
i.Enhance phagocytosis (opsonins)
ii. Complement activation



C-Cytokines

Low MW& soluble proteins | Produced in response to injury by microbes | Allow cellular communications

Cytokines regulating innate immnunity

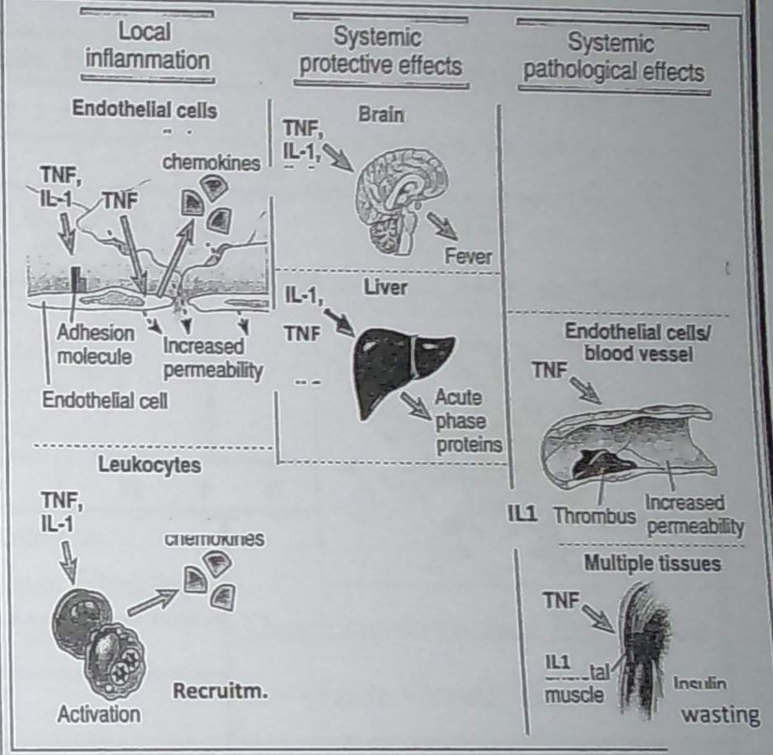
Produced mainly by ***MQ & dendritic cells***

Inflammatory cytokines			Interferons	IL10
✓ TNFα, IL1,,IL6 & Chemokines e.g IL8	✓ IL12	✓ IL18	Antivirals	Inhibitory

Inflammatory Cytokines

Produced mainly from MQ and DCs (on recognizing microbes by PAMP receptors)

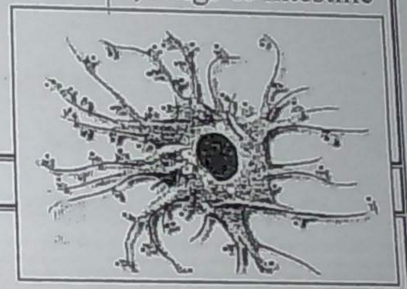
1-TNF α (Cachectin)	**2-IL1**
Sources	
i.MQ & dendritic cells	
ii.Th1	ii.Endothelial cells
Functions	
i-Acute inflammatory (phase) response a..Endothelial cells : ***VD*** (↑ permeability)&activation of ***coagulation*** ***b.Regruitment of neutrophils*** *to site of inf.&****their activation*** c.Liver : synthesis of ***acute phase proteins*** d.Hypothalamus: ***fever*** (endogenous pyrogen) e.Muscle wasting & fat catabolism → ***Cachexia***	
ii-Tumor necrosis	***ii- ⊕ of adaptive immunity*** a. ⊕ ***B cells*** Proliferation & differentiation into plasma cells b. ⊕ ***Th cells***

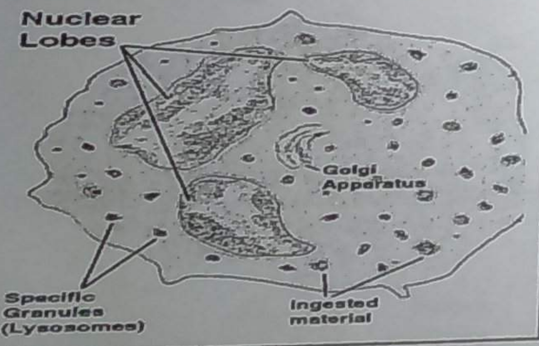


	3-IL6	**4-Chemokines**
Sources	***i.MQ , dendritic cells*** & endothelial cells	
	ii.Th2	ii.**T cells** ,platelets & fibroblasts
Functions	**i.Acute inflammatory response** : a, b &c (M)	**Migration of neutrophils & lymphocytes** from blood to site of infection
	ii. ⊕ of adaptive immunity ⊖ ***B cells*** → Proliferation & differentiation into plasma cells	

IV- Phagocytosis

Phagocytic Cells

Neutrophils	Monocytes & MQ	Dendritic cells
I- Origin : BM progenitor cells		
II - Site		
The most abundant WBCs in blood ***1st phagocytic cell*** that encounter the infection ↓ May migrate into tissue spaces ↓ **↑ in n= in acute bacterial infections** Leukocytosis (not neutrophils) ⇨ indicts → ABI	Monocytes circulate in blood ↓ **Become MQ in tissues** (mature) 	♣ **Skin** ♣ **MM** of nose , lungs & intestine 
III - Structure		
♥ Segmented nucleus ♥ **Cytoplasmic lysosomes** filled with: **i-Lysosymes** collagenase elastase ***ii-Defensins*** (EC organism / Most Bacteria)	♥ Kidney shaped nucleus ♥ **Cytoplasmic lysosomes** filled w:	Dendritic=branched like a **tree** (From Greek "dentron")
IV - Functions		
1 - Phagocytosis Ingestion & killing of bacteria (Few (TB)) and viruses.		
NO ← **2-Professional APCs** → **Activate T cells**		
	Antigene presenting cells	***Main APC : Migratory cell*** Travel to LN&spleen to ⊕T cell



Response of phagocytic cells to infection

1-If an org.invades the mechanical and chemical barriers & the effect of normal flora

Ecounter ***resident MQ & dendritic cells*** in subepithelial tissues

(When org. invades blood ⟶ encounters circulating neutrophils & monocytes).

2 - Recruitment of neutrophils from BVs to site of inf.

Resident MQ &Dendritic cells secrete ***inflammatory cytokines*** that ↑expression of adh.mol. / Cause VD &Chemotaxis

a.↑ expression of adhesion molecules by TNFα ,IL1& 6 on both

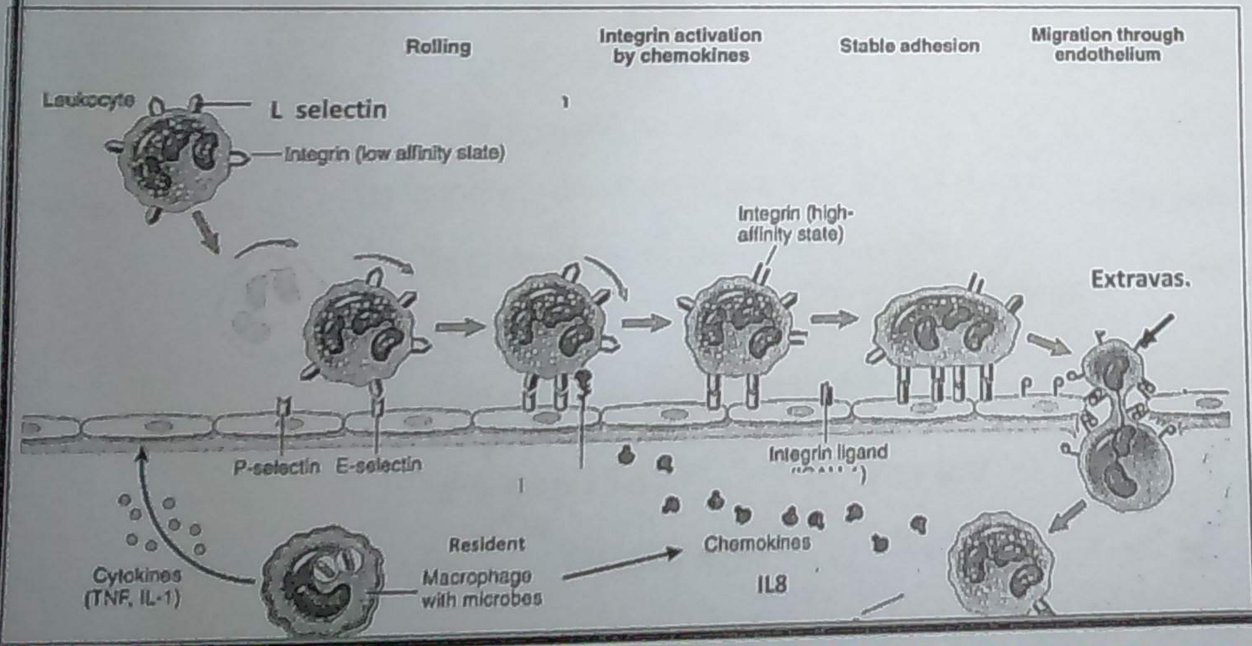
Endothelial cell surfaces

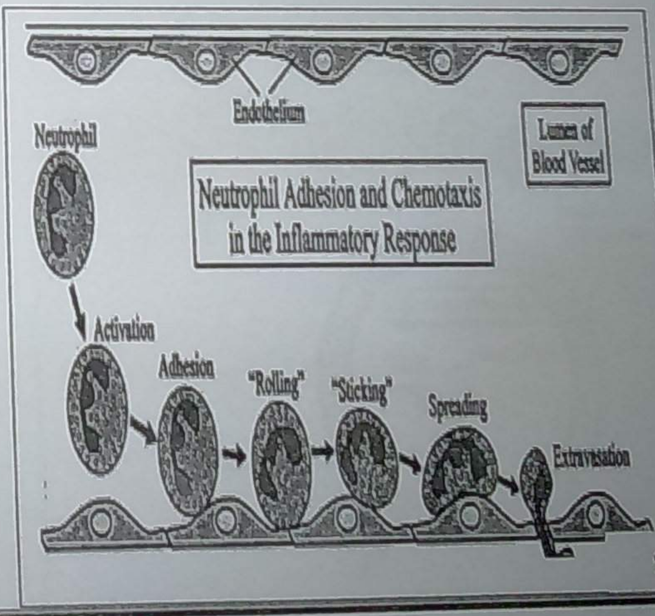
♦ E&P selectin ♦ Integrin ligand

Leukocytes

♠ L selectin ♠ Integrin

Neutrophils adhere to endothelium (***Adhesion***) ⟶ ***Rolling*** ⟶ ***sticking*** ⟶ ***spread***





b-Vasodilatation : by TNFα,IL1&6 (also by histamine from mast cell)

Loosening junctions between endothelial cells

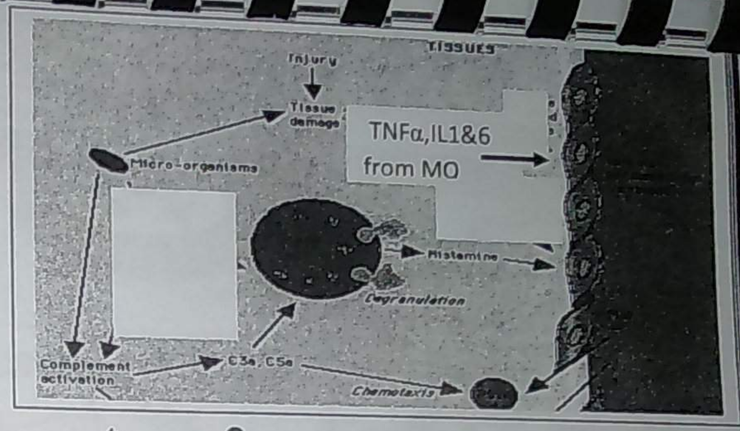
↓

Squeezing of neutrophils (***Extravasation*** or ***diapedesis***)

C-Chemotaxis

Neutrophils migrate to site of inf.attracted

by **chemotactic** substances (**IL8** & **C5a**)



Steps of Phagocytosis

Recognition	Uptake	IC killing	Outcome

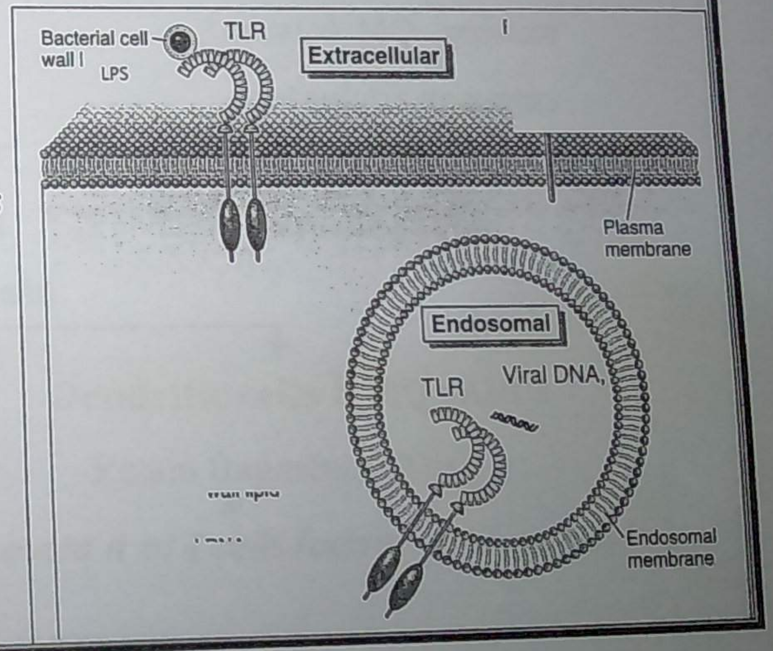
1- Recognition of microbes

by pattern recognition receptors (PRRs) of phagocytic cells

Site	Funtions	Example
•Cell surface •Endosomes	**Recognize PAMPs** (pathogen-associated molecular patterns) Charecteristic structures of microbes (not present in mammalian cells) that can't be lost or mutated	***Toll-like receptors (TLRs)***

Bacterial — LPS, Techoic acid

Viral — DNA



2 – Uptake

Attachement of bacterium to cell surface

↓

Ingestion of bacterium

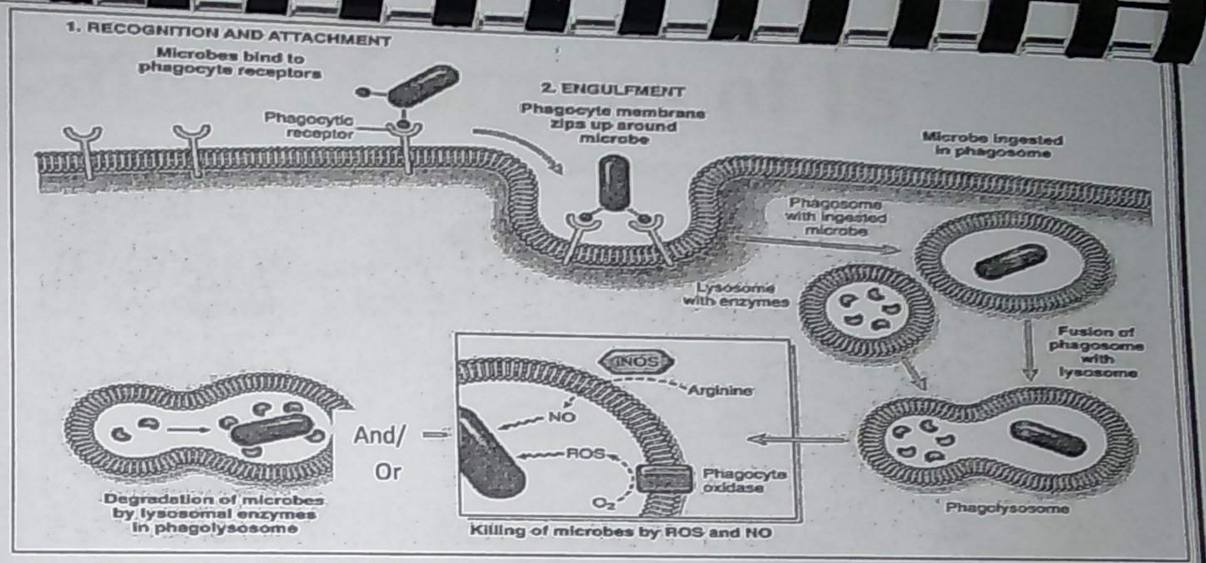
forming a **phagosome**

↓

Moves towards **lysosome**

↓

Formation of **phagolysosome**



3 – IC Killing

Oxidative killing (burst)

Molecular O_2

Myeloperoxidase | **Oxidase** – – → *Produces conditions within phagolysosomes necessary for activity of proteolytic enzymes*

↓

O_2^-, OH^- & H_2O_2 (ROS)

↓

Killing of org.

Non oxidative killing

Activated MQ produce **proteolytic enzymes** in phagolysosomes e.g **elastase**

↓

Destruction of org.

4- Outcome of phagocytosis

Neutrophils

Destroy phagocytosed particles completely

Dendritic cells & MQ : APCs

Retain fragments (Ags)

↓

Present it to T cells (adaptive immunity)

Classificatio[illegible]f organs of IS

I - Primary (Central) lymphoid organs

*Site of **development &***

***maturation** of immune cells*

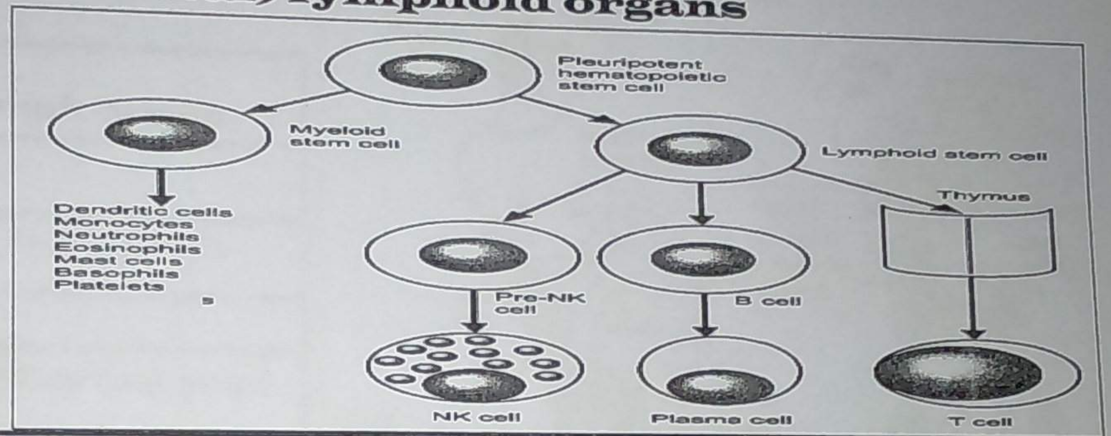
A - Bone Marrow

1-Development of all immune cells

Contains **pleuripotent stem cells**

⬇

Differentiate into cells of IS



Circulating in blood		*Residing in tissues*		*Present in tissues & blood*
• Eosinophils	• Neutrophils	Mast cells	• Dendritic cells	**Lymphocytes**
• Basophils	• Monocytes		•Macrophages	• NK cells • T& B cells

2 – Maturation of B cells

B - Thymus

Site

In front of heart &

behind the sternum

Developement

Fully developed at birth

⬇

Grows until puberty

⬇

Shrinks

Function

Maturation of T cells

T cells learn to differentiate between ***self*** (body's own cells) &

non self (foreign objects,organisms,or diseased cells)

⬇

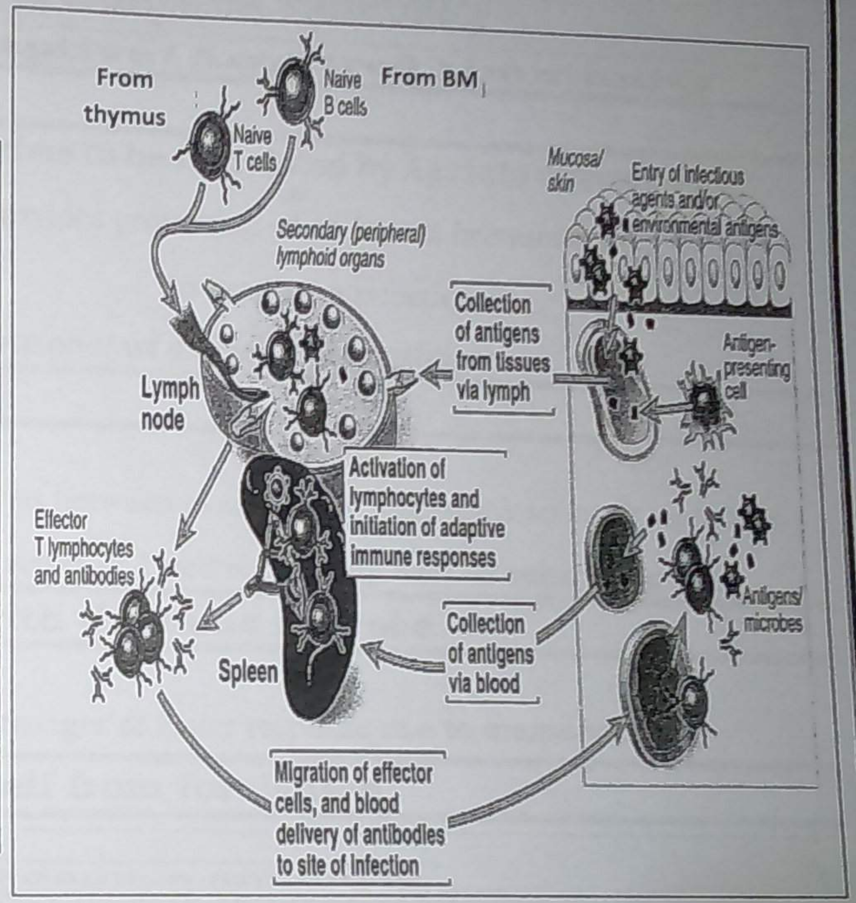
T cells recognizing self cell as **foreign are destroyed**

II-Secondary (Peripheral) lymphoid organs

Sites where immune cells ***meet, interact &***

perform their functions

1-Spleen	2-Lymph nodes
A-Cellular contents	
i. MQ , dendritic cells &lymphocytes: T, B & NK cells	
B-Functions	
1-Immunological filter of blood ⬇ Removes any foreign material or damaged cells	*1-Sample incoming lymph* (drained from tissues) ⬇ Remove any foreign material
2-Site of ⊕ of mature (naïve) B & T cells ⬇ *Differentiation into effector cells*	



3-Mucosal associated lymphoid tissues (MALT)

> 50% of lymphoid tissue in the body

Diffuse collections of phagocytes & lymphocytes

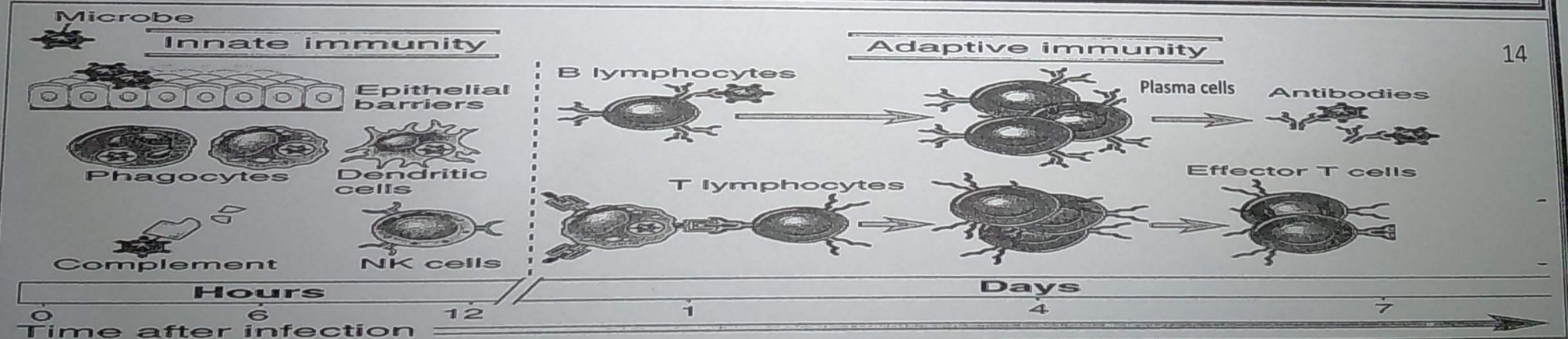
In lymphoid tissue lining GIT, RT& GUT

Well formed lymphoid follicles

Tonsils, Peyer's patches & appendix

Comparison between innate & adaptive immunity

Innate (Natural) immunity	Adaptive (Acquired) immunity
1-Time of action	
Responds immediately ⬇ **1st defense** against infections	**Takes time to be stimulated by Ags into effector cells** ⬇ Provides protection when **innate immunity fails to eradicate** infection
Both innate & adaptive immunity collaborate against any invading pathogen	
2- Specificity	
Non specific React to structures common to many microbes	**Specific** Distinguishes between even closely related microbes & molecules ⬇ Each B & T cell reacts only with ***its specific Ag***
3- Memory on Reinfection with the same microbe	
No Response with the same magnitude	**Yes** Stronger & faster response due to ***memory cells***
4- Ability to distinguish self from foreigness	



Essay Questions

1-Compare between characters of innate & adaptive immunity.

2- How can MQ recognize pathogens ?

i.By PRRs :explain .

ii.By opsonin receptors : recognize opsonins (C3b,IgG) bound to pathogens.

3-How can MQ Kill pathogens?

4- Give a short account on sources & functions of IL1 OR TNF α , OR IL6

5- Give reason :

- Normal bacterial flora are part of innate immunity

- Recruitment of neutrophils from BVs to site of infection

Immunology 2

Cell Mediated Immunity

Cell mediated IR&T cells

T cell developement	MHC molecules	Th &Tc activation	Cytokines Regulating CMI	Down regulation of IR	Immunity against microbes	Pathological effects of CMI	Deficiency of CMI

T lymphocytes deve... ...ment & Differentiation

I-Origin of T cells

From **stem cells in BM**

⬇

Circulate in blood as **immature thymocytes** with **no** surface markers

CD molecules
(cluster of differentiation)
♦Surface markers
given numbers : 1,2,3,4.....
♦Each immune cell
has specific CDs

II-Maturation of T cells: in thymus

A-Structure of thymus

Outer cortex

Packed with
***immature** T cells*

Inner medulla

T cells pass into it
during their maturation

Both are packed with a network

formed of epithelial cells, MQ & DCs

⬇

Interact physically with thymocytes

B-Thymocytes differentiation

Thymocytes differentiate into **2 types** of T cells

	T helper (Th) : CD4+ cells	**T cytotoxic(Tc) : CD8+ cells**
1-% of circulating T cells	60-65%	30-35%
2-Surface markers	**a-TCR complex** : i.T cell receptor (Ag R) ii.CD3	
	b-CD4	***b-CD8***
3-MHC restriction	Recognize Ag only in association with MHC ***class II*** 	Recognize Ag only in association with MHC ***class I*** 

III-Release of T cells

Mature T cells released from thymus are cd

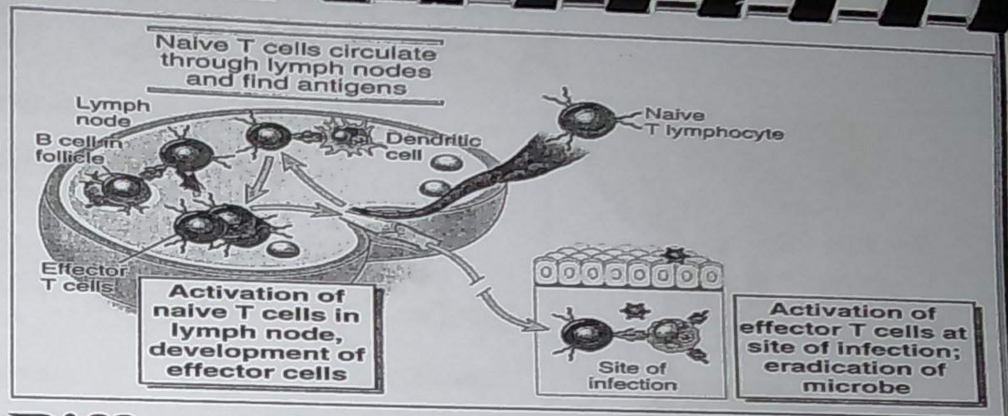
naïve lymphocytes (have never encountered Ags)

↓

Circulate to **2ry L.O**

to be ⊕ by professional APCs

(MQ, dendritic cells & B cells)



IV- Clonal expansion & Differentiation of T cells into

Effector cells

Effector ***CD4+ cells*** : ***Th1&Th2***

↓

Produce **cytokines** that ⊕ MQ&Bcells

Effector ***CD8+ : CTLs*** (Cytotoxic T lymphocytes)

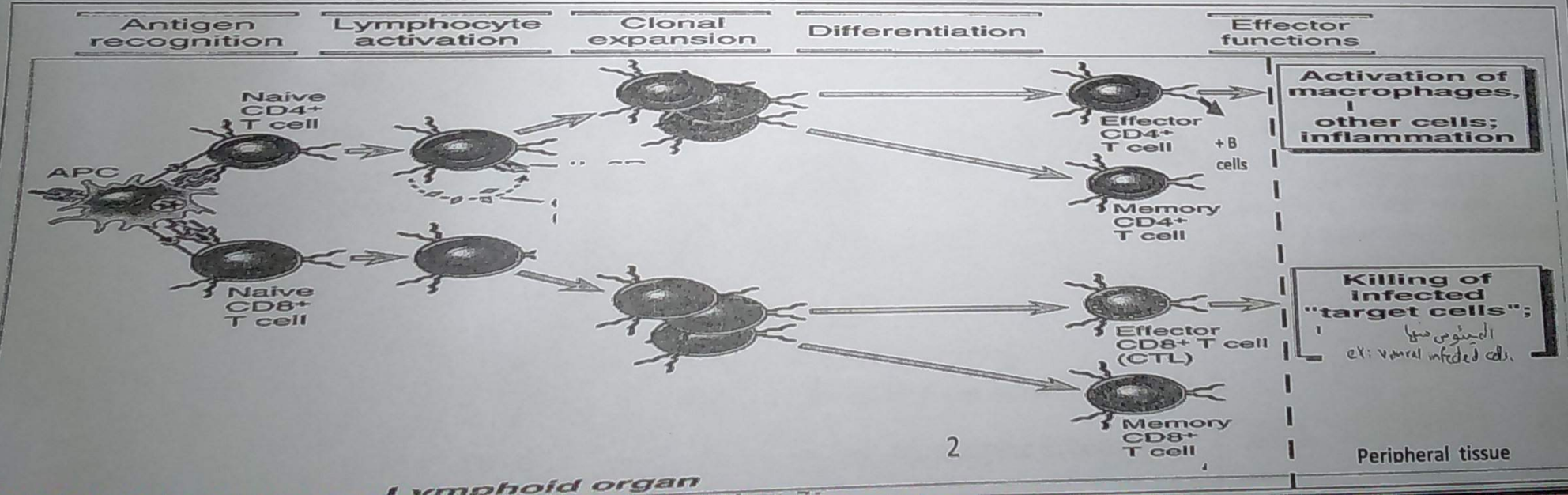
↓

Kill infected cells

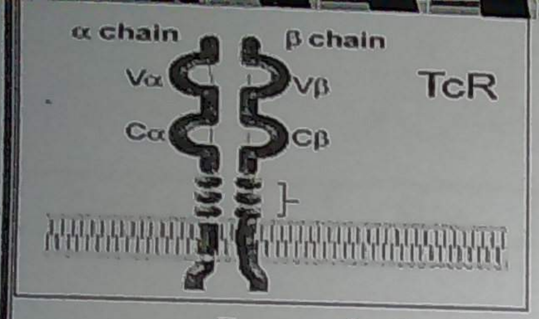
Memory cells

Memory **CD4+**

Memory **CD8+**



TCR COMPLEX



I - T cell receptor (TCR)

A-Structure & Diversity

Structure

Formed of α &β polypeptide chains having :

C region

Anchored to CM & extends into cytoplasm

V region recognizes

Specific peptide Ag (Complementary to it) *Part of MHC* mol

{Lock & key}

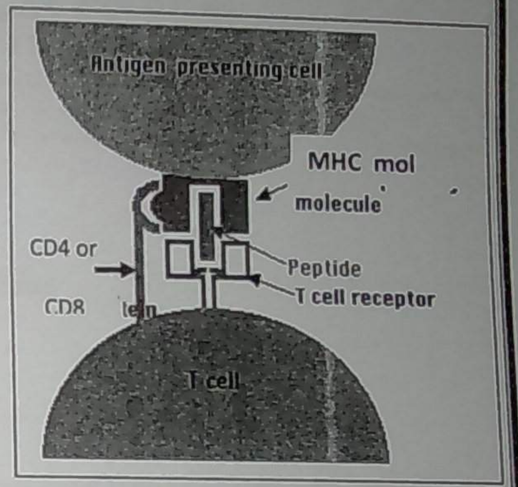
Diversity

تم تصنيع مليون قفل قبل القرض كاي مفتاح

Millions of T cells exist

React with **millions of different peptides**

Antigens



B-Positive & Negative selection

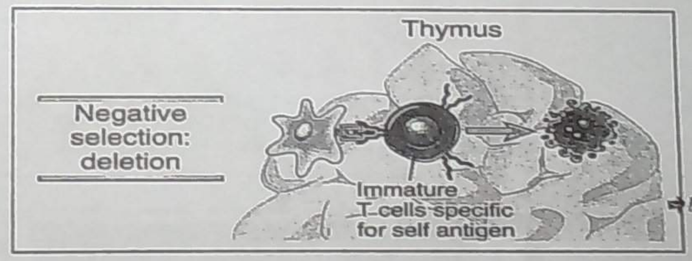
+ ve selection

T cells expressing TCR that **recognize self MHC mol.**

are selected to survive

T cells expressing TCR that don't recognize self MHC mol.

die by apoptosis



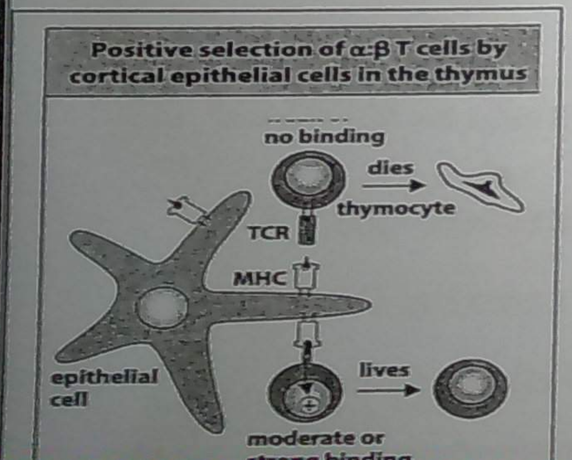
-ve selection

T cells expressing TCR that can **react with self peptides** (self reactive cells) are killed by *apoptosis*

Self tolerance

⇒ No reaction against self antigens.

No autoimmune reactions

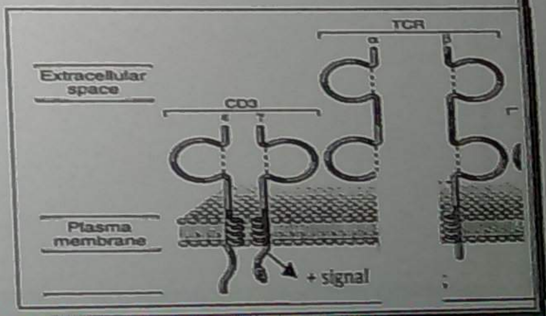


II-CD3

Associated with TCR

Transmitts signal from outside to inside

(informs that Ag receptor is occupied)



Self mol. : Major histocompatibility ... x (MHC) or human leukocyte Ags (HLA)

Definition	Site	Structure	Inheritance	Importance	Role in Ag presentation

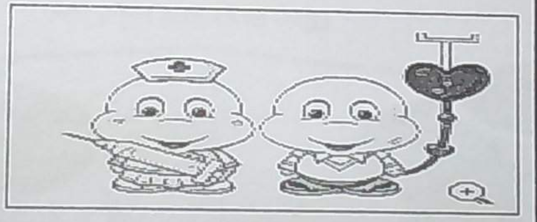
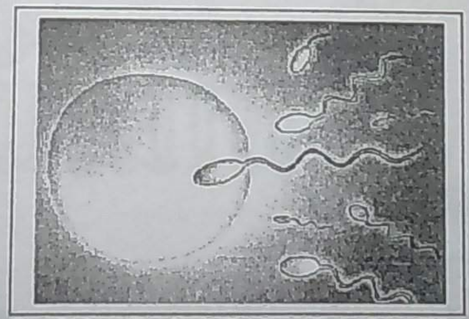
Definition

Are special inherited self proteins on **surface of nucleated cells** زي البصمة

⬇

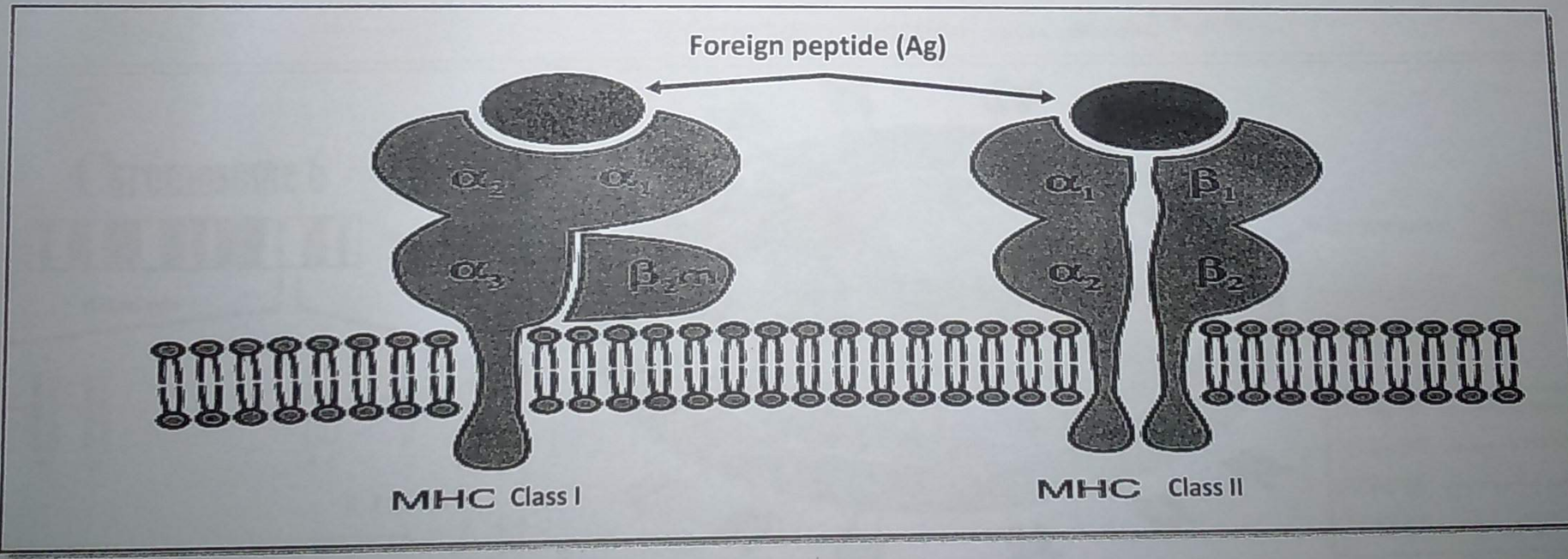
Distinguish one individual from another

Site

MHC class I mol.	MHC class II mol.
All nucleated cells (including professional APCs) ❖ ***Absent on RBCs*** ⬇ Possible **blood transfusion**  ❖ ***↓ levels on sperms & trophoblasts*** ⬇ Possible **conception & child bearing** (mother doesn't reject genetically different paternal cells or fetus) 	**Professional APCs** ♫ MQ ♫ Dendritic cells ♫ B cells

Structure

MHC class I mol.	MHC class II mol.
1-Each mol.(protein) is formed of 2 polypeptide chains : α & β (non covalently linked)	
i . α chain : 3 domains (α1, α2 & α3) ii . ***β2 microglobulin***	***i . α chain*** : 2 domains (α1& α2) ***ii . β chain :*** β1& β2
2- Ag (peptide) binding site	
Between α1& α2	Between α1 & β1



Inheritance of MHC proteins

MHC Class I mol.	MHC Class II mol.

1- MHC proteins are coded by multiple genes on short arm of chromosome 6

3 genes : ***A , C & B*** | 3 genes : ***DR , DQ & DP***

2-Each person has **2 sets of these genes :** 1 paternal & 1 maternal

3- Alleles inherited from both parents are **codominantly expressed** in each individual

4-MHC genes are **the most polymorphic genes** in human genome

A gene : 240 alleles ***B gene :*** 470 ***C gene :*** 110 | ***DR gene***: 350 alleles

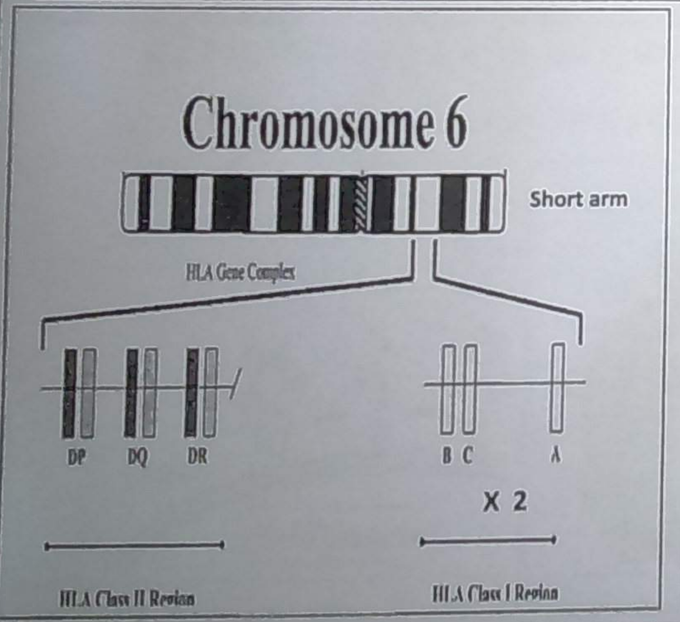
↳ different form of same gene

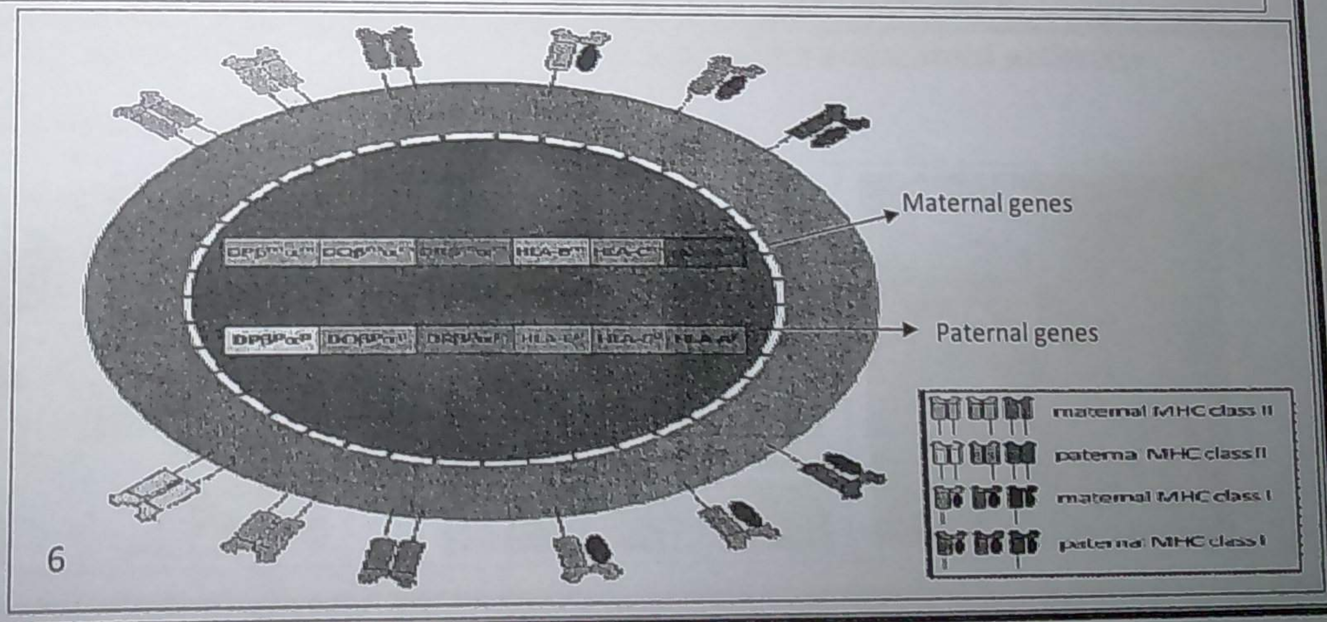
5-Outcome of MHC gene expression in different individuals

Synthesis of polypeptide molecules :

*i.**Different** in amino acid **sequence***

*ii.**Carry same function*** ⇒ Con~~te~~noad Peptide.





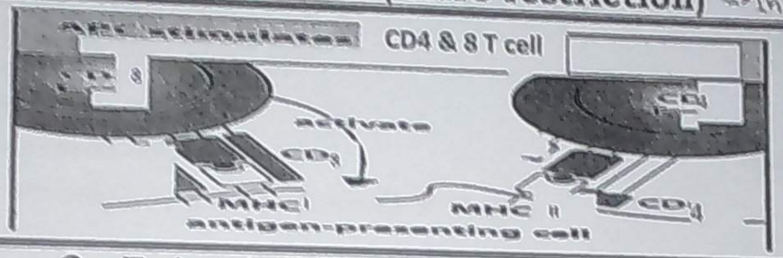
Importance of MHC mol. in health and disease

MHC class I

MHC class II

1 - ⊕ of T cells (MHC restriction) => In 2nd lymphatic organs

Tc cells recognize foreign peptide only if associated with ***MHC mol. Class I***



Th cells recognize foreign peptide only if associated with ***MHC mol. class II***

2 - Rejection of transplanted organs

Foreign MHC class I & II on donor tissue transplants are **recognized by IR of recipient**

↓

Transplant ***killing & rejection***

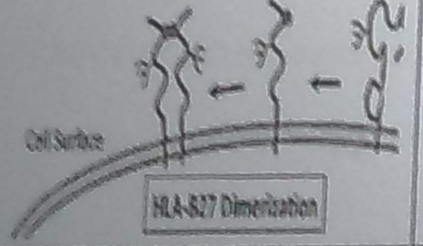
↓

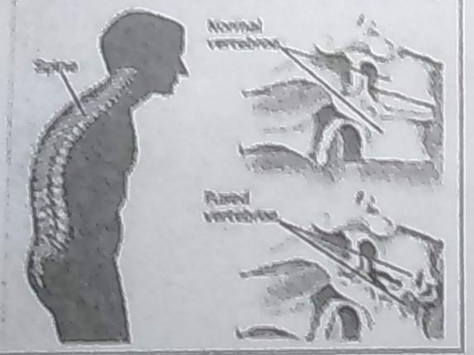
MHC mol.must be **closely matched as possible** between donor & recipient

3-Association of some MHC alleles with certain autoimmune diseases

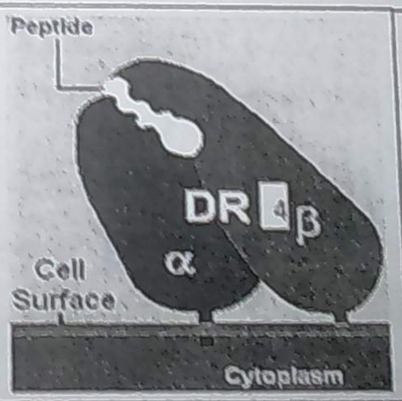
B27 in **90%** of pts with **ankylosing spondylitis**

(B27 is present in only **10%** of normal persons)





DR4 in pts with **rheumatoid arthritis**



Functions of APCs

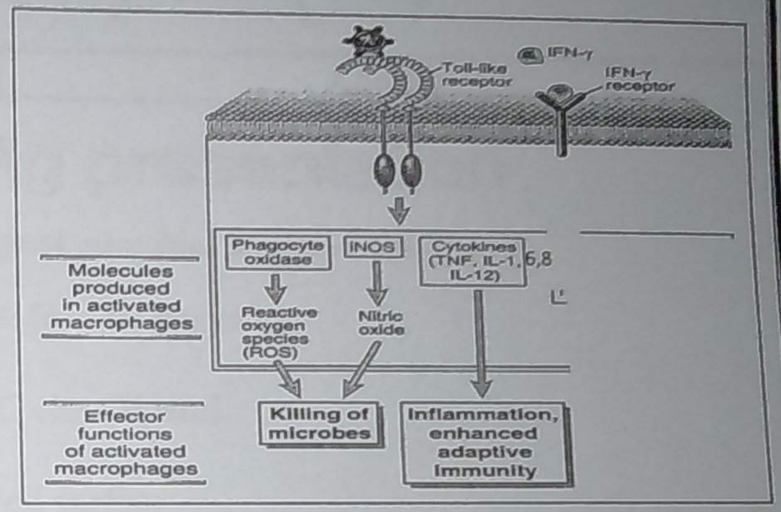
1- Recognize any microbe via PAMP receptors (PRR)

↓

Phagocytose & kill it (phagocytic cells)

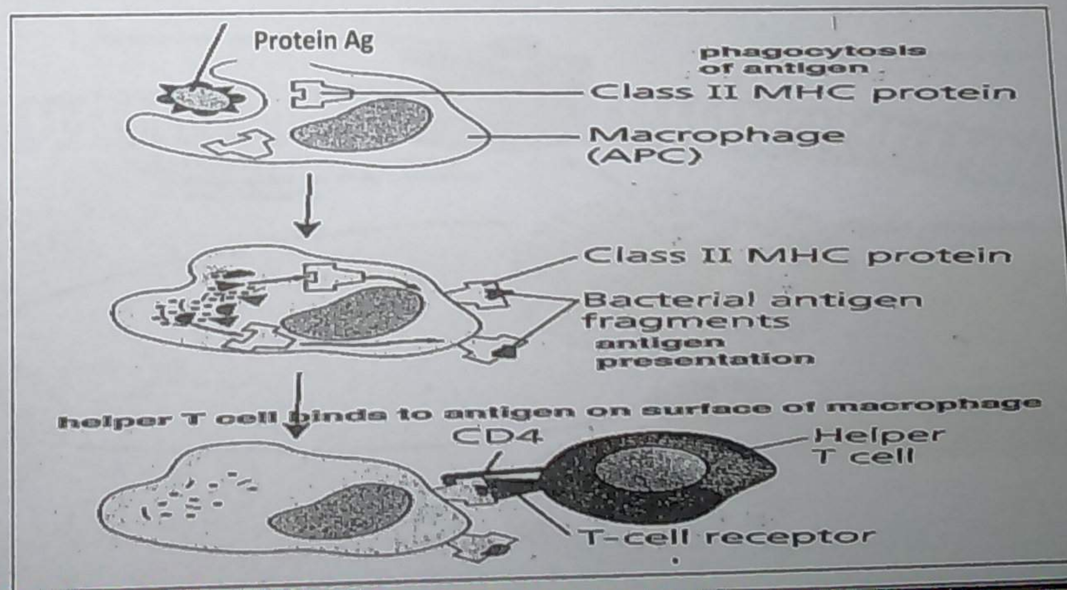
2-Inflammation

- ***Acute inflammatory response*** → TNFα , IL 1& 6
- ***Chemotaxis of neutrophils & T cells*** → IL 8



3-Activation of T cells : by

- ***Ag presentation***
  - Digest phagocytosed particle
  - into **fragments**
  - (by special enzymes)
  - ↓
  - Fragments are associated with
  - MHC class **II mol.**
  - ↓
  - Transported & displayed on cell surface
  - ↓
  - Recognized by **CD4+Th cells**
- ***Production of IL 1*** (⊕Th) ***& IL 12*** (induce formation of Th1)



CD4 T helper lymphocytes (Th)

Role of MHC class II	Activation	Anergy

Role of MHC class II in Ag presentation

Professional APCs (MQ , dendritic and B cells) **ingest** microbial proteins (Ags)

⬇

Degrade (chop) it into fragments (peptides) by enzymes

⬇

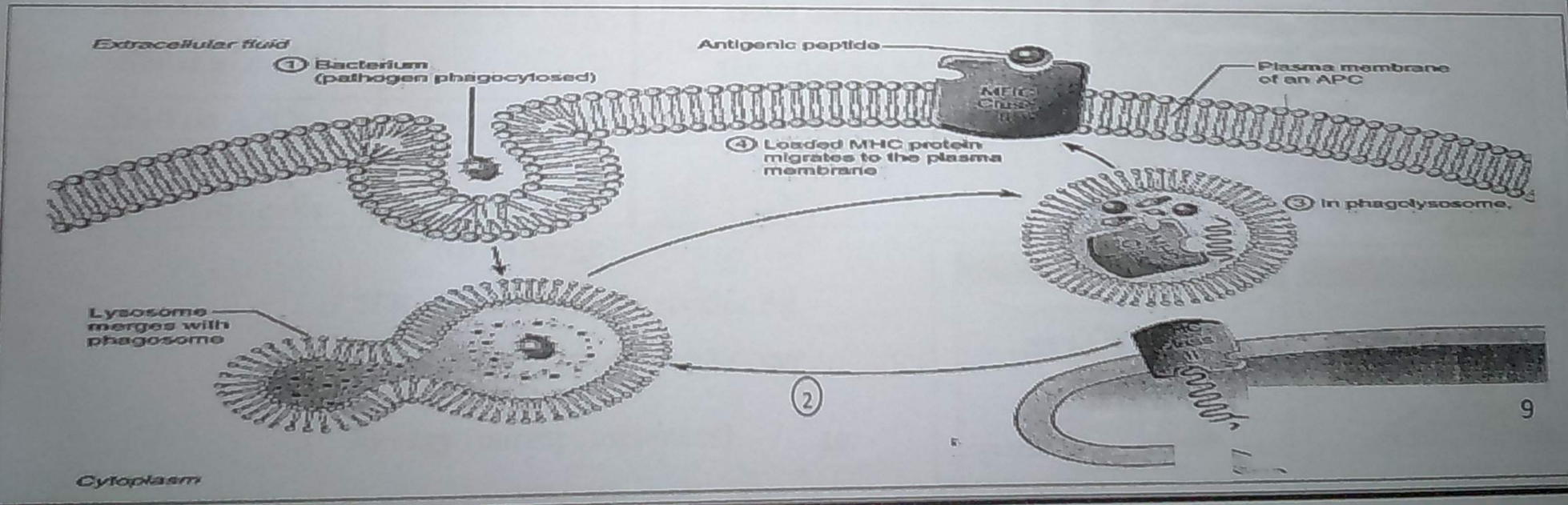
Fragments are associated withMHC class **II mol.**

⬇

Transported & displayed on cell surface

⬇

Recognized by **CD4+Th cells**

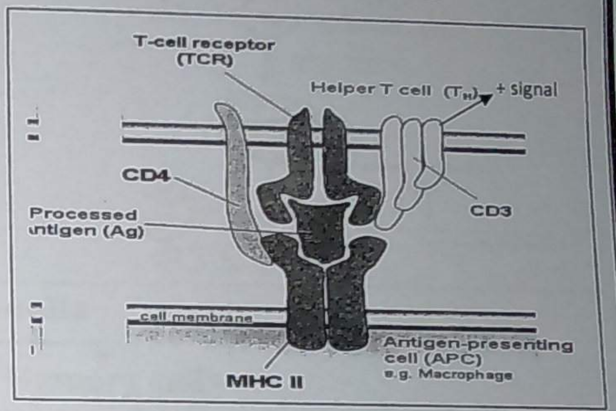


Activation of CD4 Th cells

I - Activation of naïve Th cells

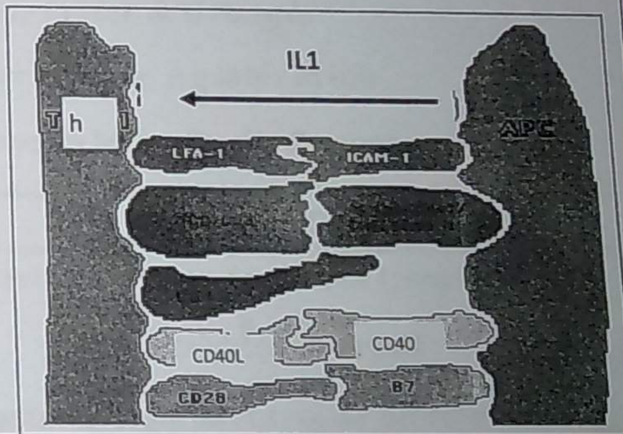
A-Recognition of Ag

TCR recognizes	CD4	CD3
its specific Ag presented in MHC **Class II** mol. **on APCs**	Interacts with MHC mol.**class II** ⬇ **Stabilizes** interaction of TCR with its specific Ag	Transmitts **IC activation signal**



2- Co-stimulatory molecules needed for activation

i.B7 on APCs	Interacts with	**CD28** on Th cells
ii.ICAM-1on APCs (Intercellular ad.mol.1)	Interacts with	**LFA-1** on Th cells (Leuc.func.ass.Ag 1)
iii.CD40 on APCs	Interacts with	**CD40L** on **activated** Th cells
iv.IL1 from MQ & dendritic cells	Activates	Th cells



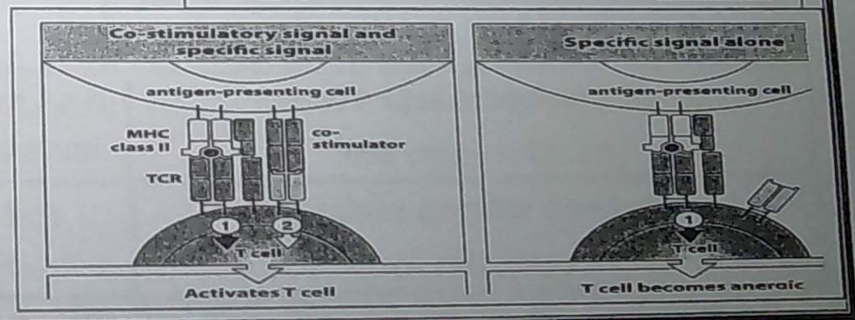
NB Anergy

If TCR interacts with its specific Ag

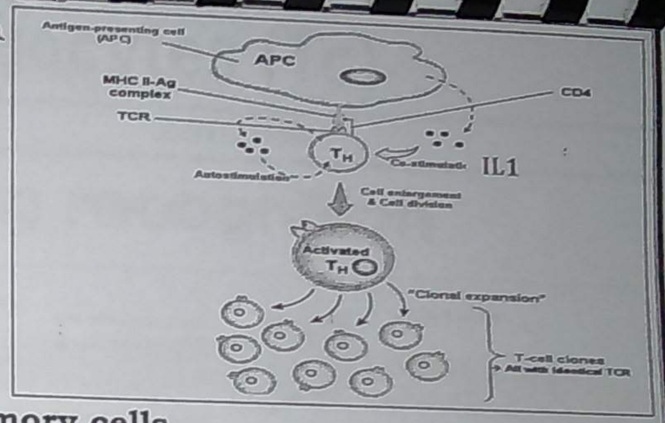
& *costimulatory signals don't occur*

⬇

Anergy (unresponsiveness)



II-Consequences of naïve Th cell activation



A-Clonal expansion

Once activated , naïve T cell replicate

⬇

↑n= of Ag specific T cells

⬇

Cope with microbial replication

B-Differentiation into effector cells & memory cells

Effector cells

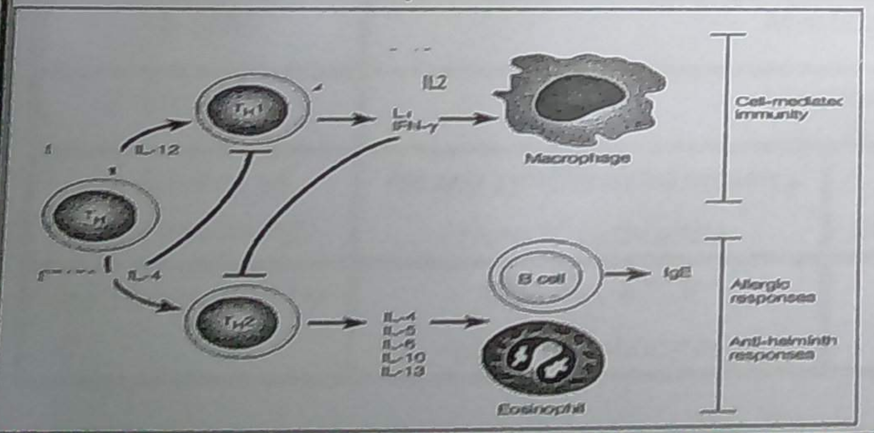
Th1 ⟷ **Th2**

For rapid elimination of Ags

⬇

Secrete different cytokines

IL2 &IFNγ	IL4,5,6,10&13
⊖ MQ,NK,Tc&B cells	⊕ B cells, eosinophils ⬇ **Helminthic** immunity &**allergy**



Memory cells

Responds ***faster & stronger***

on encountering same Ag **later in life**

✓ **Comparison between Naïve T cells & memory T cells**

Naïve T cells	Memory T cells
1-Generated and act during *1ry IR*	Generated during **1ry IR** but remain *inactive* ⬇ Activated in ***2ry IR*** ⬇ **Faster & vigorus** response on re-exposure to same Ag even eve after years
2-Require more Ag & more costimulation	Require ***Less*** amount of *Ag* & *less costimulation*
3-Produce less cytokines	Produce ***greater amounts*** of *cytokines*

CD8+ T Cytoto ymphocytes (Tc)

Role of MHC class I	Activation

Role of MHC class I in Ag recognition

Cells infected with IC pathogens :

Viruses , or IC bacteria (e.g Mycob.TB))

synthesize new viral or bacterial proteins **(Ags)** in their cytoplasm

↓

Degrade it into fragments (peptides) by enzymes

↓

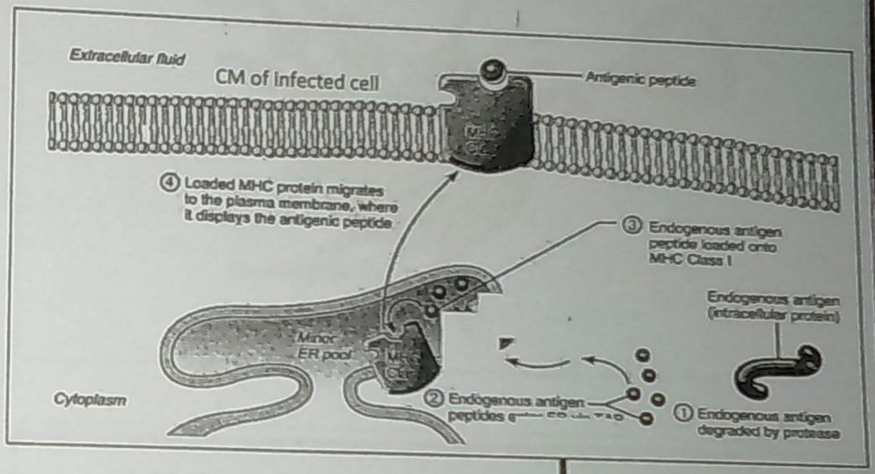
Fragments are associated with MHC class ***I mol.***

↓

Transported & displayed on cell surface

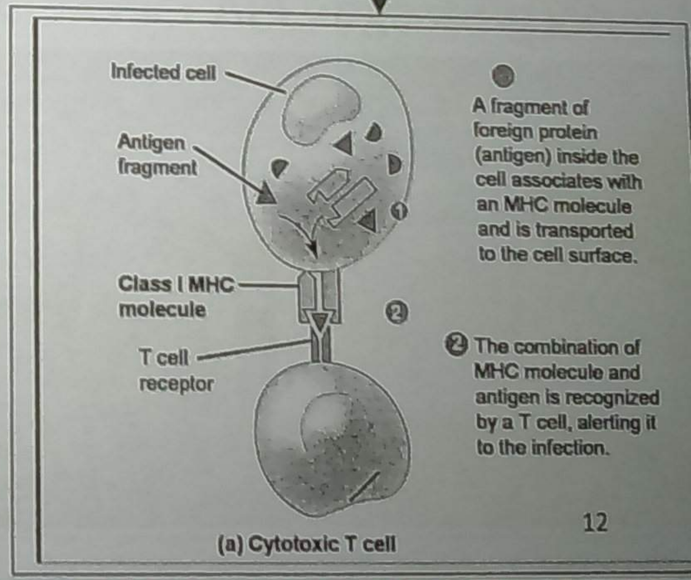
↓

Recognized by ***CD8+CTLs***



✓ **Compare between MHC class I &II molecules**

	MHC class I	MHC class II
1-Site	Mention	
2-Structure	Mention	
3-Source of expressed Ag	***Newly synthesized*** proteins from ***IC*** pathogens	Fragments of ***phagocytosed*** particles
4-Recognized by	***CD8*** mol &TCR on ***Tc*** lymphocytes	***CD4*** mol&TCR on ***Th*** lymph



♦**ICB eg TB survive**

Mostly inside normal cell → Infected cell must be killed by ***CTL & NK***

In MQ → MQ must be activated by IFN from Th → Activated MQ **kill phagocytosed ICB**

♦**VIC must be killed by CTL & NK**

(to ⊖ viral multiplication & spread)

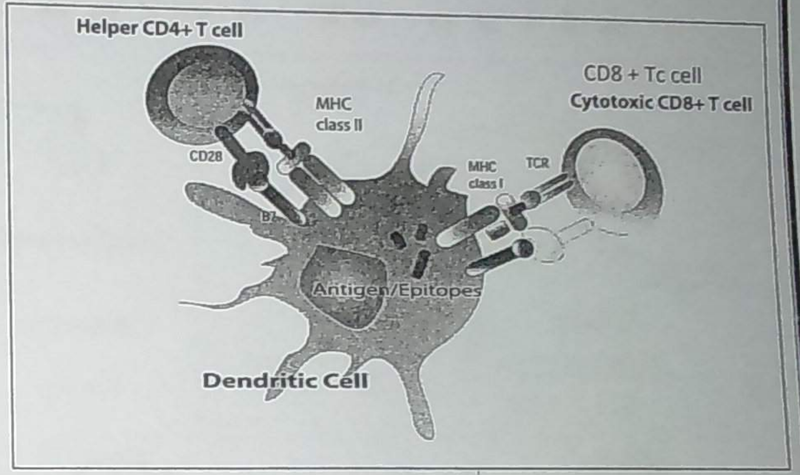
In case of IC pathogens, APCs present Ag with ***both MHC class II&I***

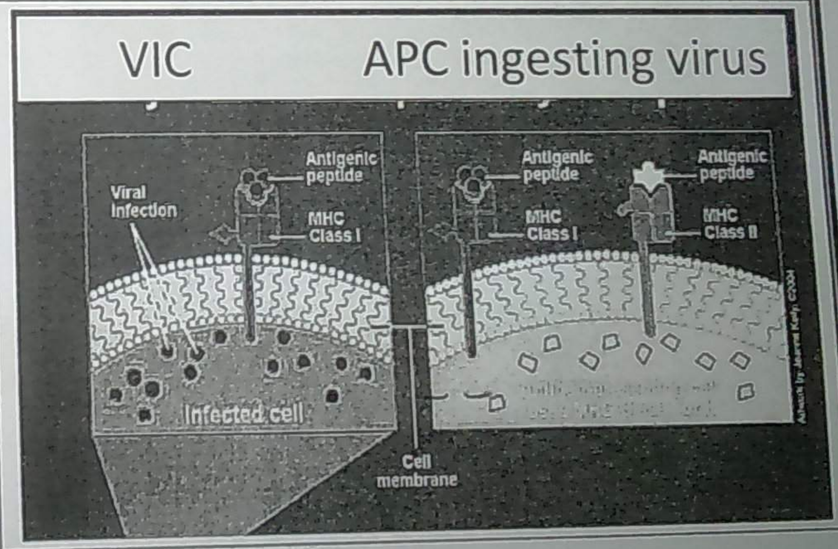
⊕ ***both Th & Tc.***

In case of EC pathogens, APCs present Ag with **MHC class II only**

⊕ **Th only**

ECB (most of bacteria) : live mostly outside the cell



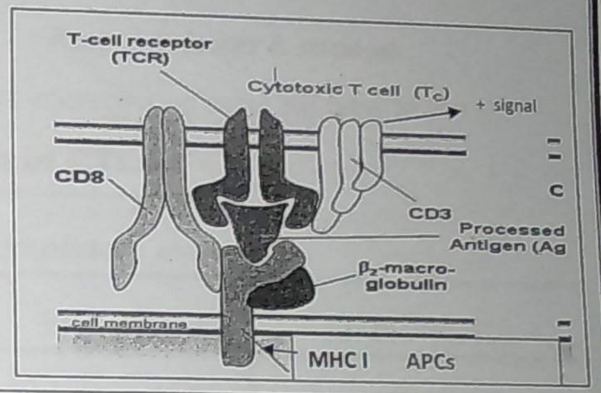


Activation of CD8 Tc cells

I - Activation of naïve Tc cells

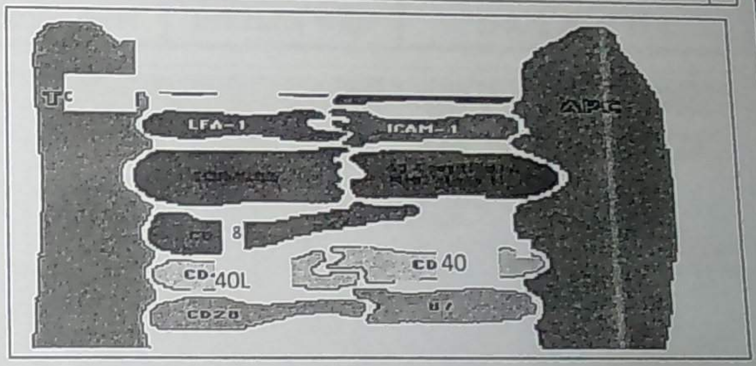
A-Recognition of Ag

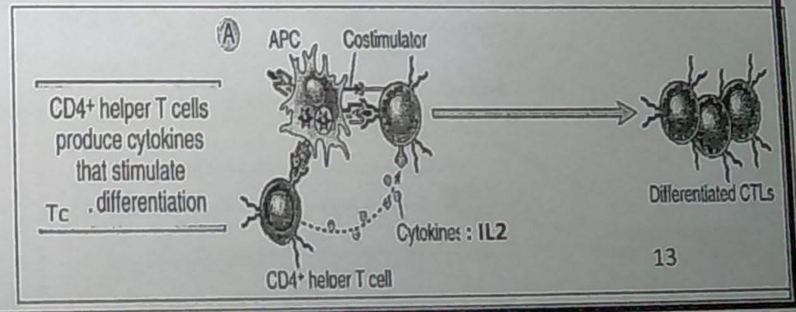
TCR recognizes	CD8	CD3
its specific Ag presented in MHC **Class II** mol. **on APCs**	Interacts with MHC mol.**class I** ↓ **Stabilizes** interaction of TCR with its specific Ag	Transmitts **IC activation signal**



B- Co-stimulatory molecules needed for activation

i.B7 on APCs	Interacts with	**CD28** on Tc cells
ii.ICAM-1on APCs	Interacts with	**LFA-1** on Tc cells
iii.CD40 on APCs	Interacts with	**CD40L** on **activated** Tc cells
iv.IL2 from Th1	Activates	Tc cells





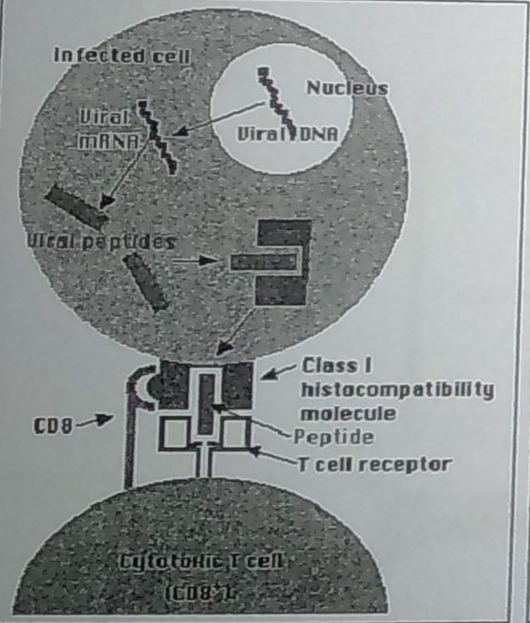
C-Activated Tc replicates &differentiates into

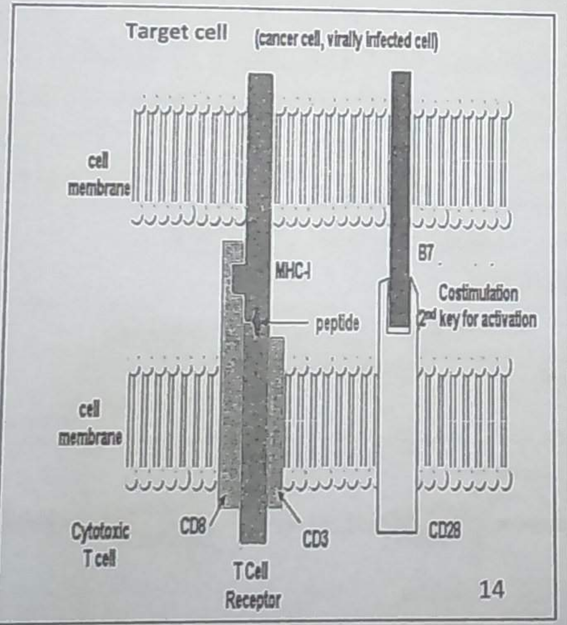
- **Effector CTLs**
- **Memory cells**
  - Responds ***faster & stronger***
  - on encountering same Ag **later in life**

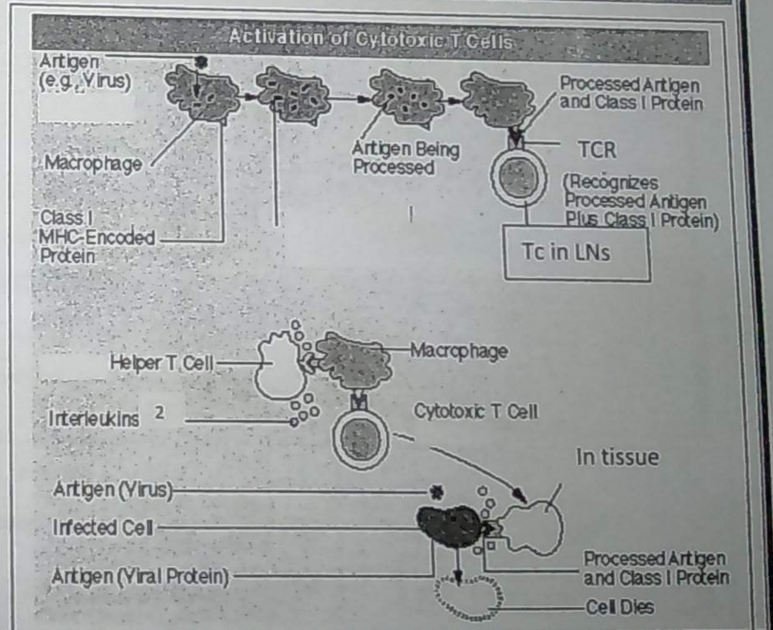
D-Target recognition & costimulation of CTLs

- ***TCR***
  - recognizes **endogenously synthesized** Ag in association with MHC **class I** mol on the surface of **target cells**
- ***Costimulatory molecules***

i.B7 on target cells	Interacts with	**CD28** on CTLs
ii.ICAM-1on target cells	Interacts with	**LFA-1** on CTLs







II-Killing of target cells by effector CTLs (EC killing or cytotoxicity)

❖ *Occurs by **apoptosis** by one of 2 ways*

Perforin pathway

On binding to target, CTL granules fuse with its CM

↓

Release of ***perforins & granzymes*** into intercellular space

↓

Perforins form **pores** in target cell

↓

Granzymes **enter** the cell

↓

Apoptosis

CD95 or Fas-FasL pathway

Activated CTL expresses FasL protein(CD 95L)

↓

Binds with ***Fas protein on target***

(Transmembrane receptor or CD95)

↓

Apoptosis

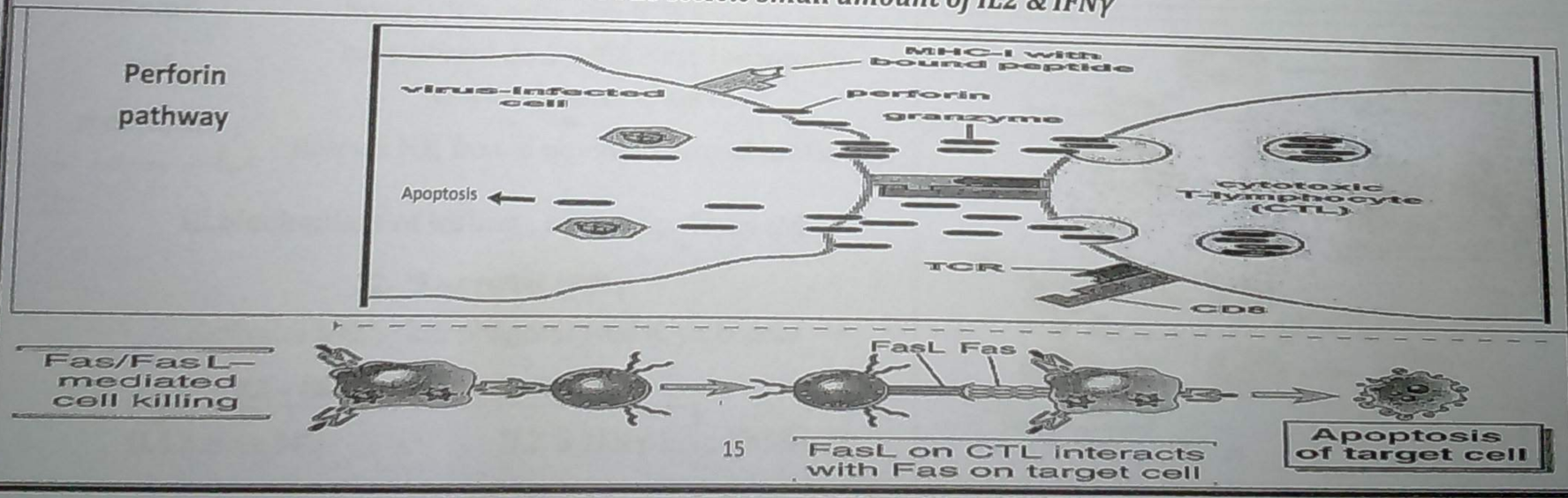
↓

❖ Killed target cell is phagocytosed & destroyed by **surrounding MQ**

↓

Destruction of any microbe (e.g virus) inside it

NB. CTLs secrete ***small amount of IL2 & IFNγ***



Natural killer (NK) cells

A-Characters

- **Size**: Large granular lymphocytes
- **Maturation**: BM
- **Markers**: ♦ CD16 ♦ *CD56*

B-Functions

1-Direct EC killing (cytotoxicity)

i.Importance

Destroy ***large*** particles that ***can't phgocytosed*** by phagocytic cells

e.g VICs,cells with IC bacteria&tumor cells

ii.Target recognition : recognize cells that

- **Express altered self molecules**: Some VICs, cells with ICB & tumor cells have ***absent or ↓ MHC class I expression*** as a mechanism of survival
- **Don't express some self molecules** MHC I: Release NK from a **normal state of inhibition**

Foreign antigen without MHC

iii.Mechanism of killing : ***perforin*** pathway (M)

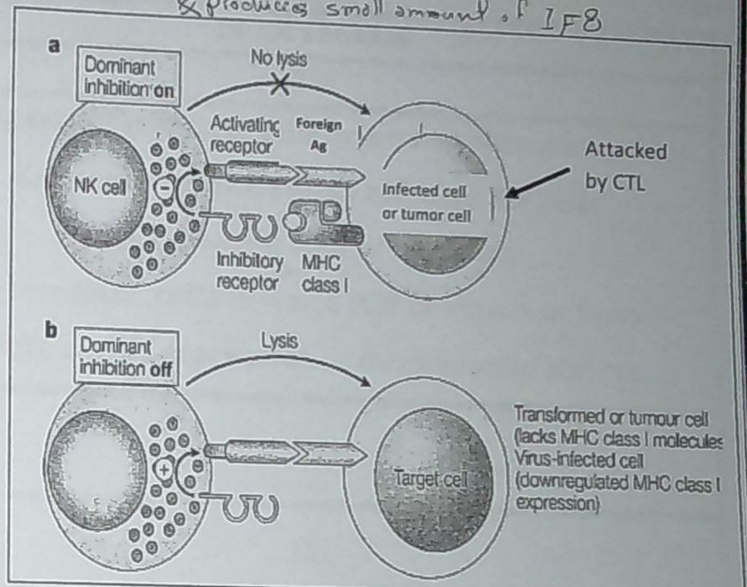
2- Secrete IFNγ

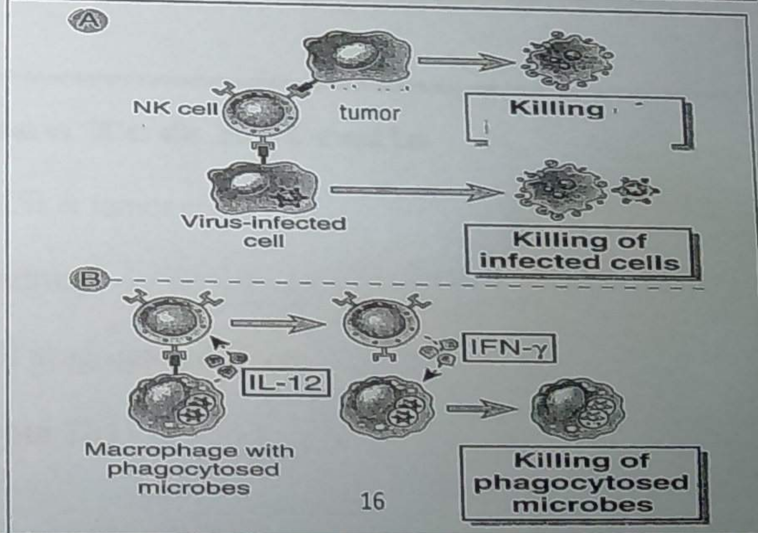
Activates **MQ** to kill **phagocytosed IC** pathogens

C - Stimulated by

- **IL12** from MQ
- **IL2 & IFNγ** from Th1&CTL

& produces small amount of IF8





Differences between Tc & NK cells

	Tc	NK cells
1-Maturation	Thymus	*BM*
2-Target recognition	**i.Ag specific** : by TCR ii.Recognizes target **expressing MHC class I** + foreign Ag	***i.Not specific :*** recognize cells expressing altered molecules ***ii.Absence of MHC class I releases NK cells*** from a normal state of inhibition ↓ NK recognize **cells** in which ICB or viruses or tumor ***↓ MHC class I expression*** as mechanism of survival
3-Mechanism of killing	CD95 or Fas-FasL pathway	*No*
4-IL2 production	Yes	No
5-Memory cells	Yes	*No*

Common features between Tc & NK cells

1- Targets : VICs , Cells with ICB & tumor cells

2- Kill by **perforin** pathway.

3-Produce IFNγ which ⊕ MQ to kill phagocytosed IC org.

4- Stimulated by **IL2 from Th1**

Cytokines regulatin ... II (Adaptive immunity)

Type II IFN	IL2	TNF β	TGF β

Type II IFN (IFNγ)

A-Sources

Th1(main) | CTL | NK

B-Functions

1-On MQ (main)

i.↑ cidal activity

Kill phagocytosed ICB

ii.↑Ag presentation

- ↑ Ag processing
- ↑ expression of MHC classI, II & costimulatory mol.

2-On Th1

↑ differentiation &+ve feedback :

IFNγ produced from Th1

⊕ MQ&dendritic cells

More IL12 production

More Th1 &⊖ generation of Th2

3-On B cells

i.Proliferation & differentiation

into plasma cells

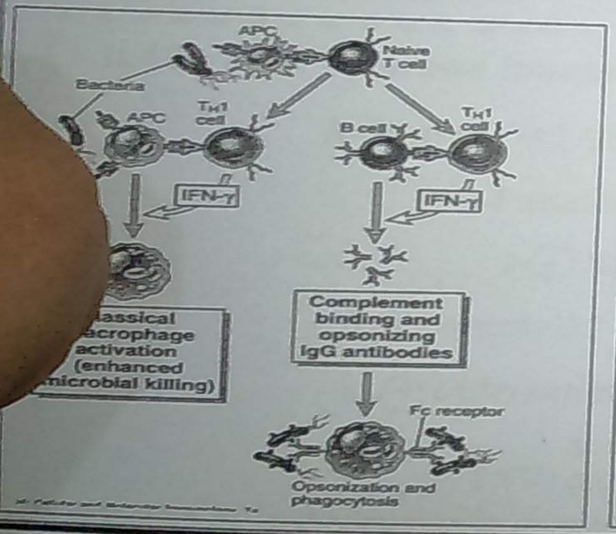
secrete Abs

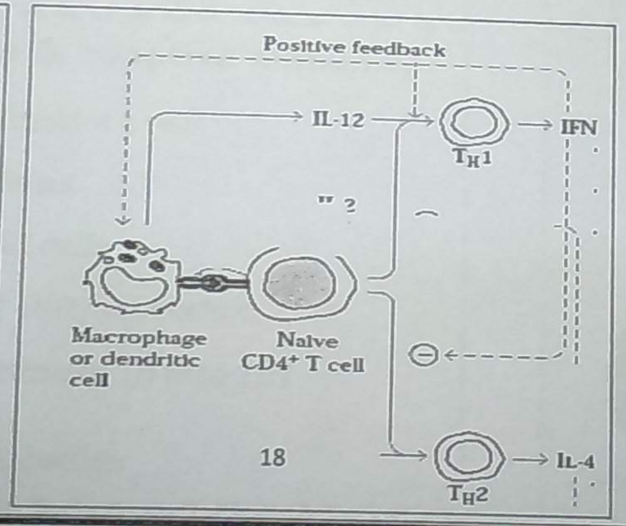
ii.Isotype switch to IgG

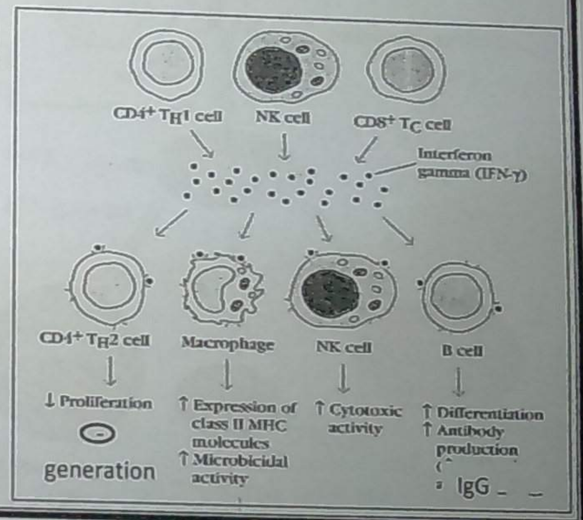
Complement activation & opsonization

4-On NK & CTL

Enhance activity





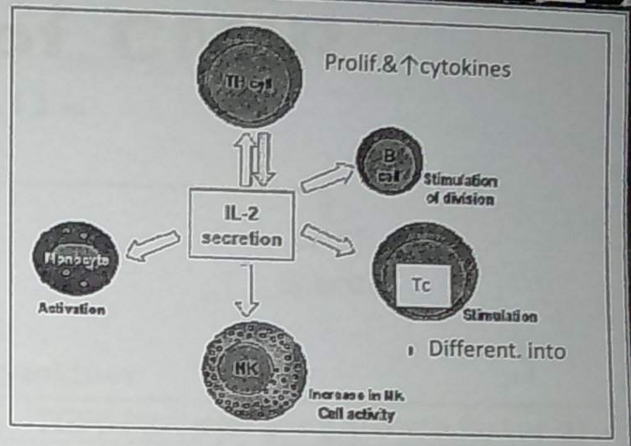


IL2

A-Sources : Th1(main) &CTL

B-Functions

On NK	On Tc	On Bcells	On Th1	On MQ
Activation	Differentiation into *CTL*	***i.Proliferation & differentiation*** into plasma cells ⬇ secrete Abs	***i.↑proliferation*** ii.↑cytokine synthesis	Activation



TNF β (Lymphotoxin)

A-Source : Th1

B-Functions : as TNFα

⊕ neutrophils & endothelial cells ⟶ ***Coagulation &inflammation***

IL12 : Link between innate & adaptive immunity

A-Source : MQ & dendritic cells

B-Functions

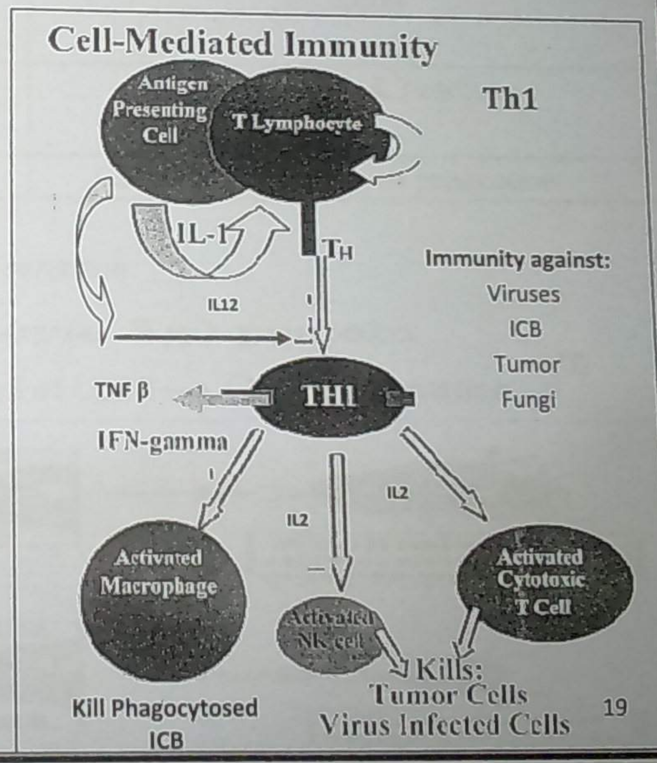
1-⊕ NK cells

↑ cytotoxicity &↑ INF γ production

2- ⊕ Differentiation of Th into Th1

⬇

↑IFNγ production



Down regu ion of CMIR

I-Regulatory T cells

A-Markers

- **CD4**: 5-10% of CD4+ cells (The remaining are T helper (90%))
- **TCR**: Ag specific
- ***CD25***: Specific

B-Functions

1 - Immune suppression : by inhibitory cytokines

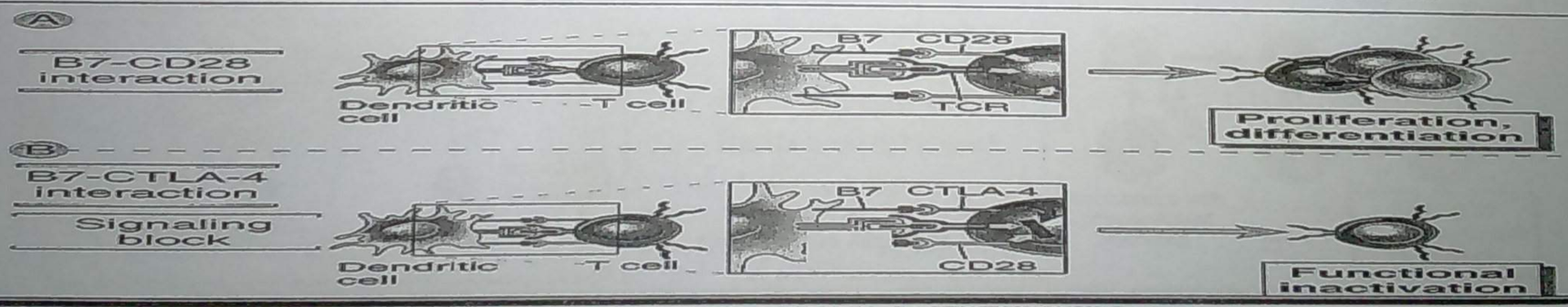
	IL10	TGFβ (transforming growth factor β)
a.On MQ	i. ↓ IL 12 production ii.↓ MHC class II &costimulatory mol. ⟶ ↓ Ag presentation	Inhibition
b.On T cells	i. ↓ IFN γ production from Th1 ii.↓ expression of costimulatory mol.	⊖ proliferation & functions
c.On B cells		⊖ proliferation & Ab production

2 - Prevent autoimmune ds

In 2nd lymphoid organ ⊖ ***self reactive clones that escaped – ve selection*** ?!

II- CTLA – 4 (Cytotoxic T lymphocyte Ag) protein

Appears on ***activated*** T cells (CD4+& CD8+) ⟶ **Binds B7 instead of CD28** ⟶ ⊖ ***T cell activation***



Immunity against microbes

Rules of defense against microbes

Innate immunity
Early response

Adaptive immunity
Effector cells & Abs ⟷ ***Memory*** **cells**
Eliminate microbes — Protection from subsequent inf.

Survival of microbe in host
By ***evasion*** or ***resistance*** to immunity

Types of microbes

IC bacteria	Viruses	Fungi	EC bacteria	Parasite
CMI *only* imm.	CMI *main* imm.	CMI *main* imm.	Humoral **only** imm.	Humoral **main** imm.

Immunity against IC bacteria

A- Innate immunity

Phagocytes

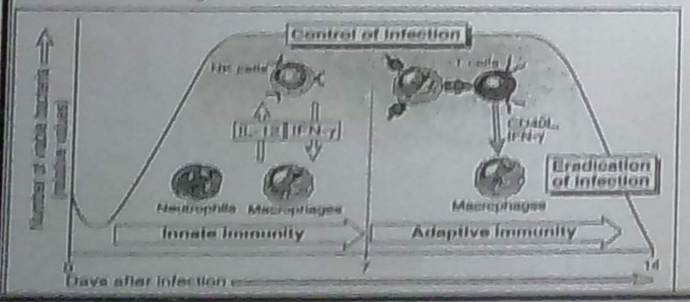
1st neutophils then MQ ingest bacteria
↓
Try to destroy them
↓
Pathogenic ICB ***resist degradation***

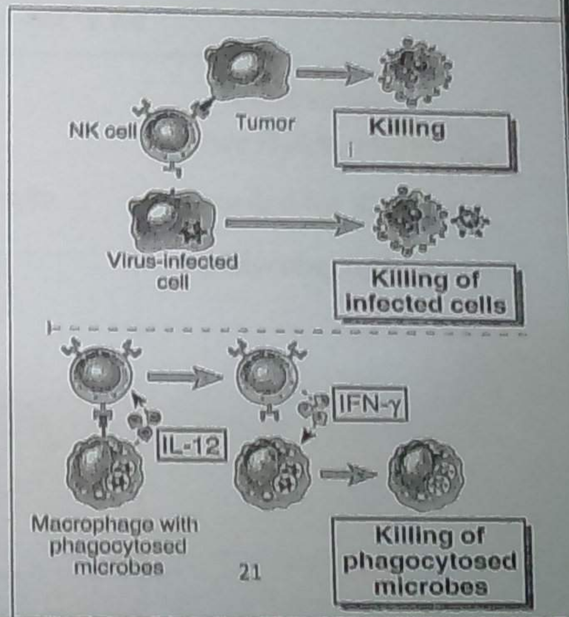
NK cells

Produce IFNγ
⊕ MQ to kill phagocytosed ICB

Kill cells with ICB having ***absent or ↓ MHC class I expression*** as a mechanism of survival
↓
Release NK from a normal state of inhibition

✓ Innate immunity **only limits** bacterial growth for sometimes
↓
Eradication requires CMI





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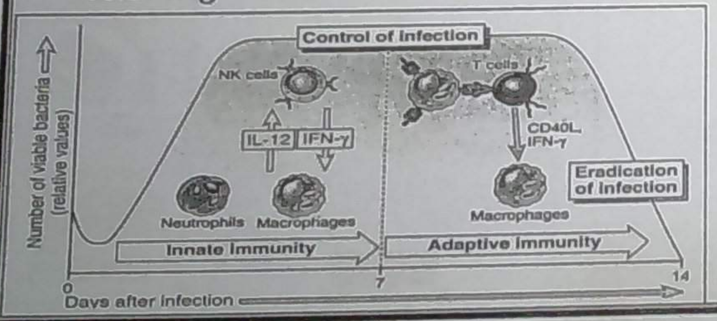
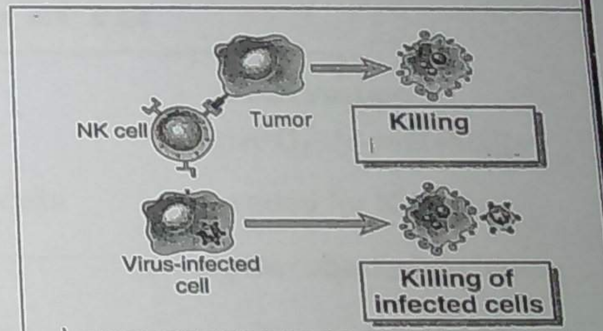
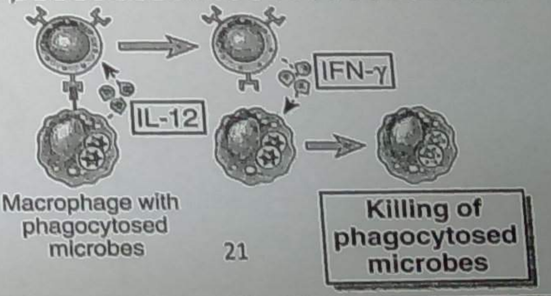






B - Acquired immunity

CMI is the main immunity against ICB

CTL kill cells infected with ICB

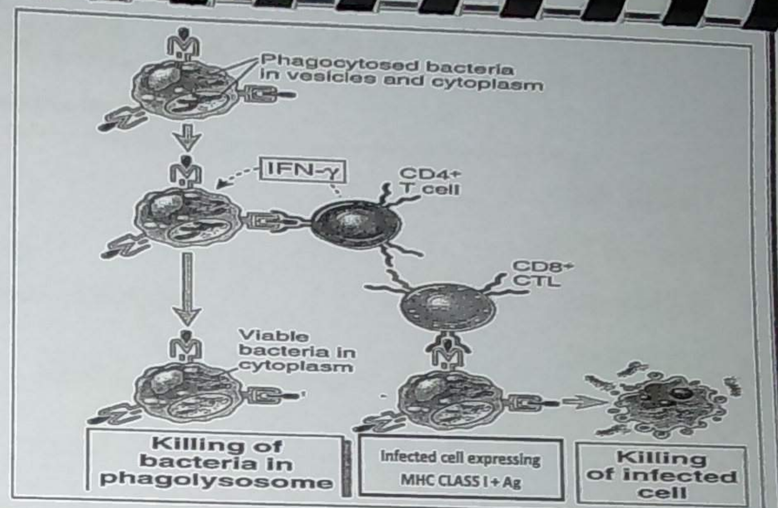
as they express foreign Ag in association with ***MHC class I***

Th1 secrete IFNγ

⊕ MQ to kill phagocytosed IC bacteria

♣ *Pts with **CMI deficiency (e.g AIDS)***

*are highly susceptible to **infection with ICB***



C - Mechanisms of evasion of IR

Disruption of phagosome

Escape into cytoplasm

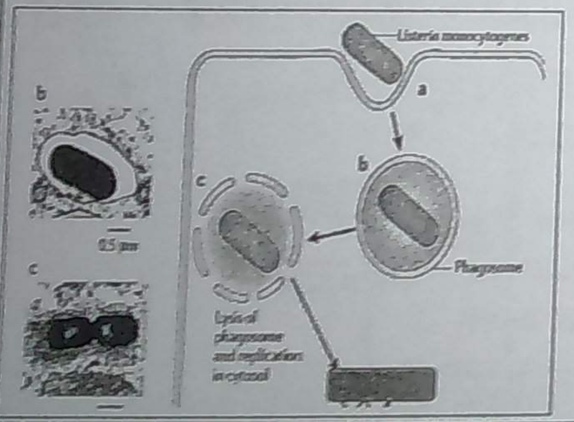
e.g **Listeria**

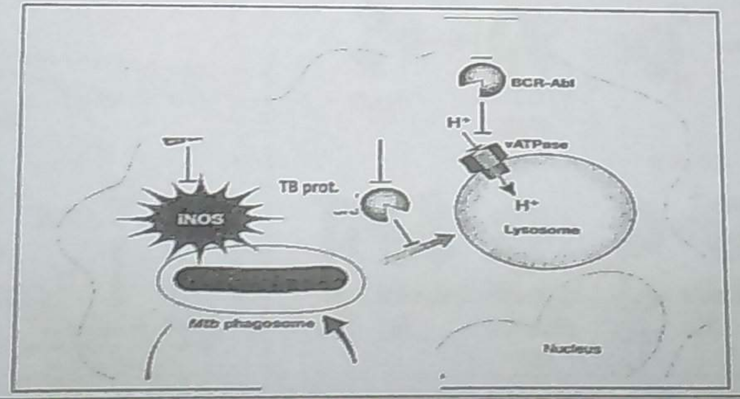
Inhibition of phagolysosomes formation

e.g ♣ **Mycobacterium TB** ♣ **Legionella**

Inactivation of reactive O_2&N_2 metabolites needed for IC killing

e.g **Mycobacterium leprae**





Immunity against viruses

A - Innate immunity

Type I interferon (IFNα & β)

Source

IFNα ↔ IFNβ

- ♦MQ
- ♦VICs
- ♣Fibroblasts
- ♣VICs

Functions

The most potent antiviral cytokine

- ⊖ **Viral replication** (antiviral state) in both *infected* & *uninfected adjacent cells* by shutting down **protein synthesis**
- **Enhance killing of VICs**
  - ⊕ NK & CTL
  - ↑*exp.of MHC class I* → Recognized &killed by CTL

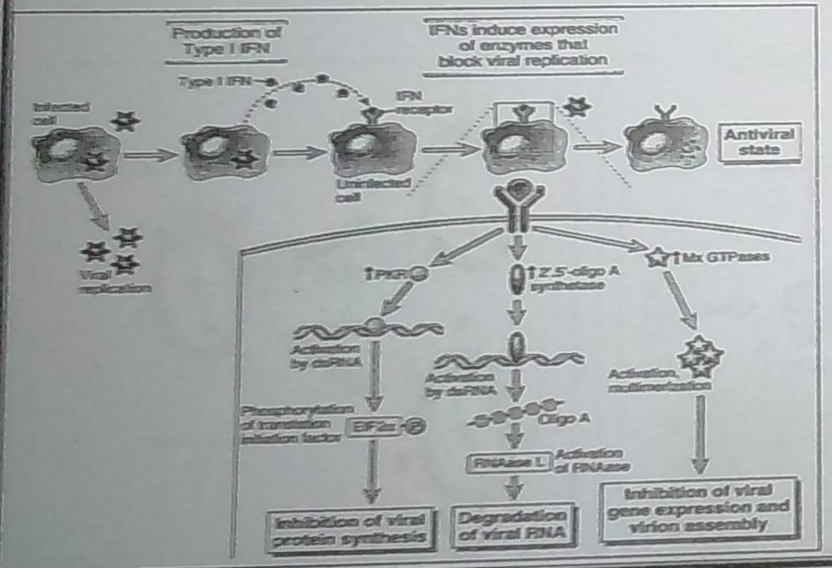
NK cells

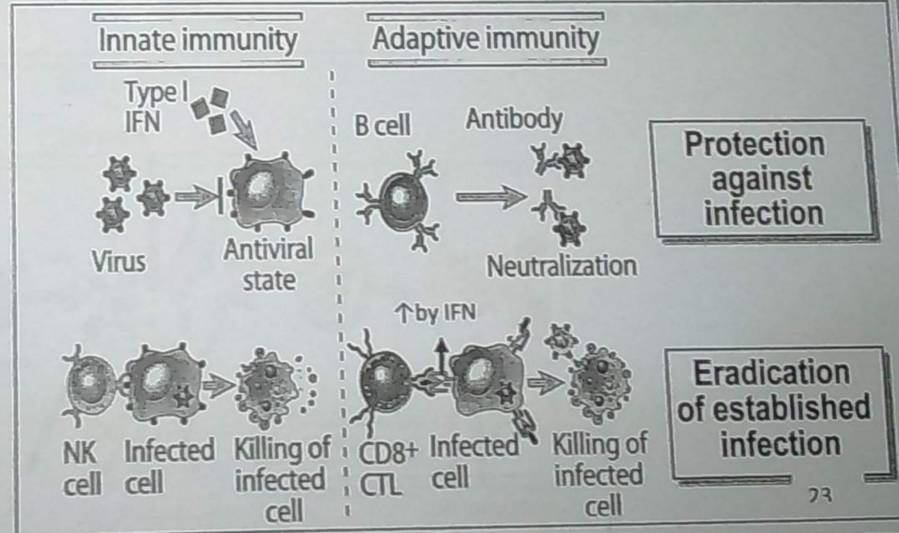
Kill VICs having

absent or ↓

MHC class I

.....





B - Adaptive immunity

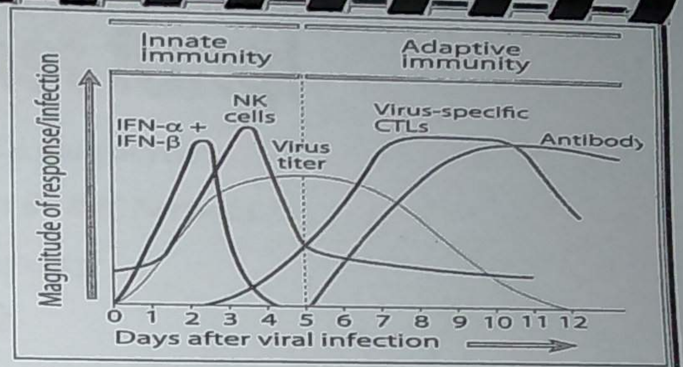
1-CMI is main immunity against viruses

CTLs (CD8+) kill VICs as they express

foreign Ag in association with ***MHC class I***

☻ *Pts with **CMI(e.g AIDS)** are highly susceptible to **infection with viruses***

2-Humoral immunity : see later

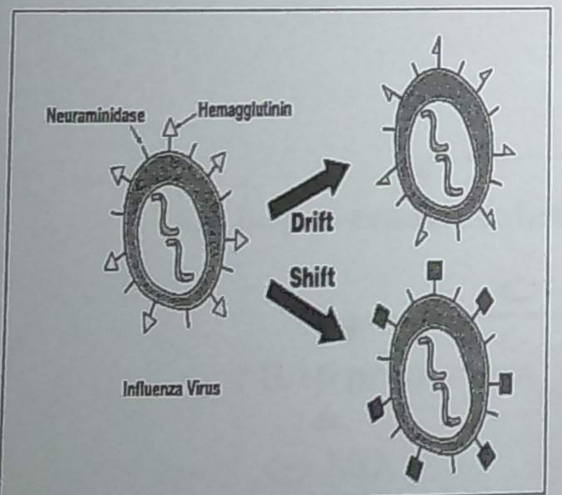


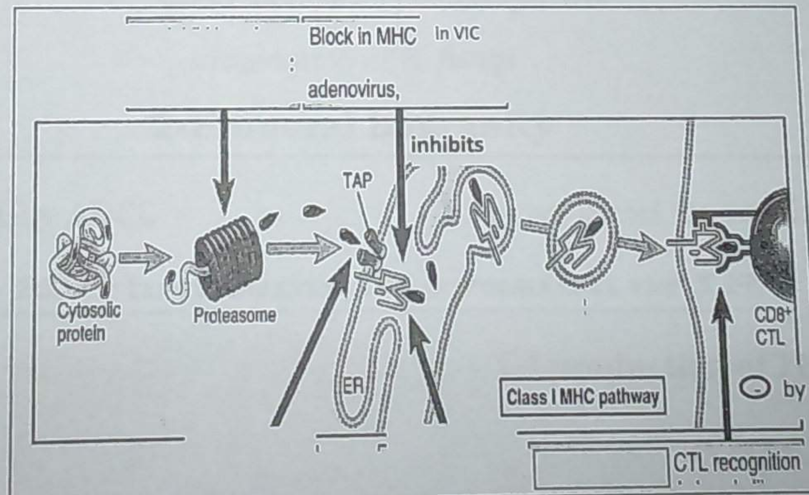
C - Mechanisms of evasion of IR

Alteration of Ags
No longer targets of IR
e.g **Influenza virus**

Inhibition of Ag presentation
By ↓ MHC class I expression
e.g **Adenovirus**

Production of inhibitory protein similar to IL10
⊖ MQ&dendritic cells → ⊖CMI
e.g **Epstein-Barr virus**





Immunity against fungi

Fungi may live **in EC tissue & within phagocytes**

↓

IR is a combination of responses ***against EC & IC bacteria***

A - Innate immunity

Neutrophils & MQ

↓

Neutrophil deficiency due to BM suppression → ↑ fungal infections

B - Adaptive immunity

1-CMI is the main immunity

Same mechanisms against ICB:

MQ, CD4+ & CD8+ cells cooperate

↓

Elimination of ***IC fungi***

2-Humoral immunity

Abs help to **eradicate inf. by ADCC**

Abs are useful for **serological diagnosis**

C - Mechanisms of evasion of IR

↑ IL10 production

↓

⊖ MQ

⊖ **production of TNF α & IL 12**

from MQ

Pathologica ffects of CMI

Septic shock by superAgs	Type IV hypersensitivity	Autoimmune ds

SuperAgs

A-Special Characters & Effects

They **aren't processed** by APCs

↓

Bind to MHC **classII** outside Ag binding groove

↓

Bind only to ***V region*** *of a particular β chain of TCR*

↓

⊕ ***large n= of Th*** cells with different Ag specificities

(**Non specific or polyclonal activation**)

↓

↑↑release of IFNγ & IL2

↑↑ release of IL1,12 &TNFα from MQ → **Septic shock**

T cells become ***refractory*** to⊕ → **Anergy**

B-Examples

Bacterial toxins

Staph.aureus

• Enterotoxins

•Toxic shock syndrome toxin

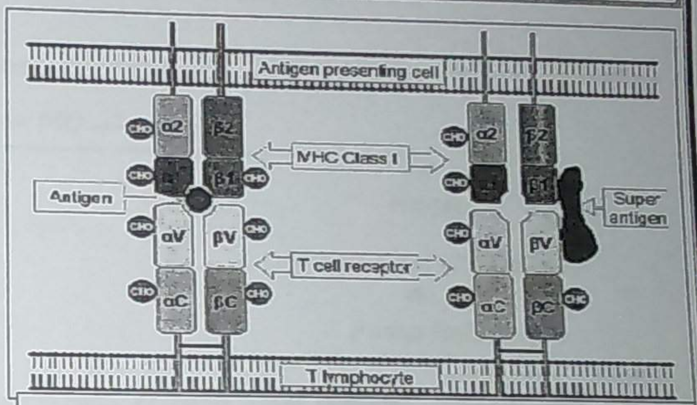
Strept.pyogenes

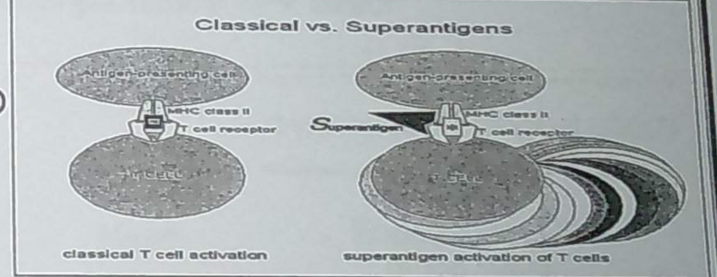
Pyrogenic toxins

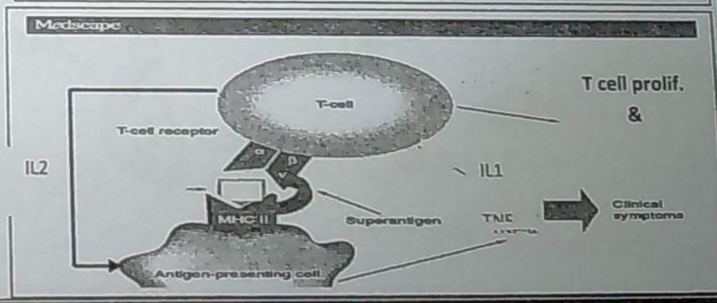
Viral proteins

• Epstein Barr V

• Rabies V







Septic Shock

Definition

Cytokine –induced pathological consequences of **superAgs**

Mechanism

↑↑ release of IFNγ & IL2 from ⊕ large n= of Th cells with different Ag specificities

↑↑ release of IL1, 12 & TNFα from MQ → act on

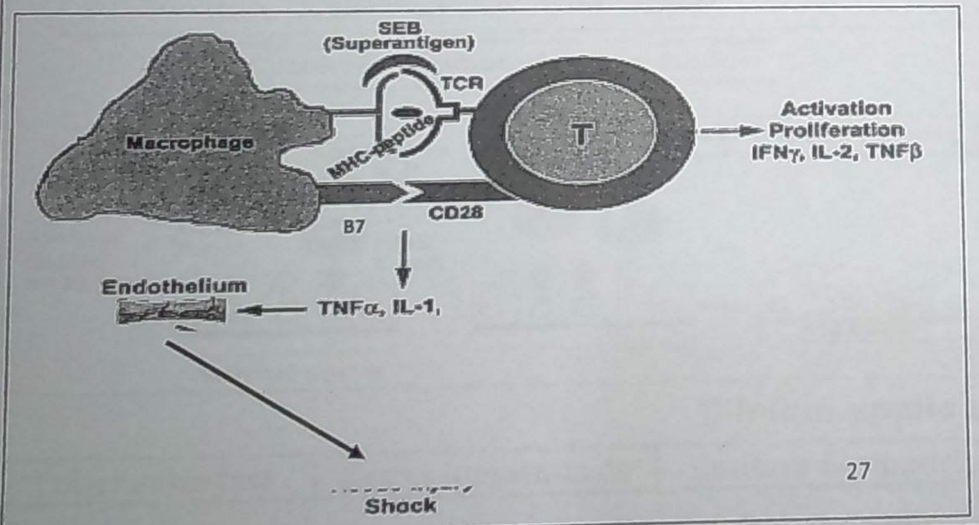
Endothelial cells

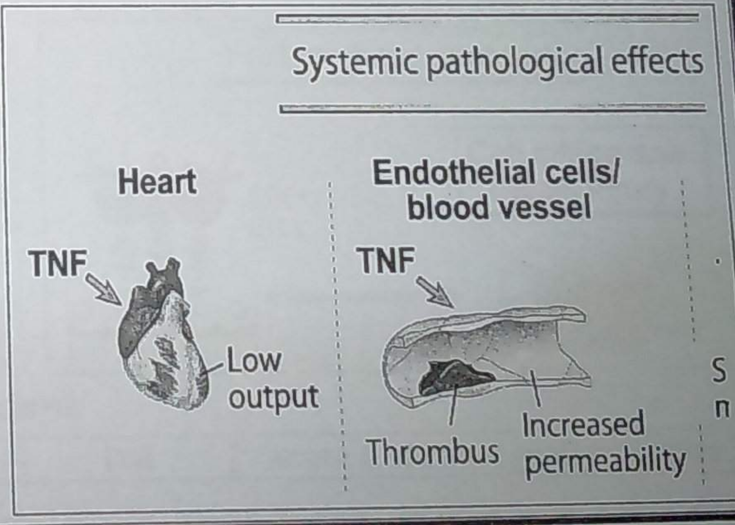
- Systemic VD → ***Hypotension***
- ↓ synthesis of anticoagulation factors → ***DIC***

Heart

- ↓ myocardial contractility → ***Pump failure***

Hypoperfusion of liver , kidneys & CNS → **Multiorgan failure** → **Death**





Hypersensitivity

Definition	Time	Classification (according to mechanism of injury)	
Exagerated IR resulting in tissue damage	2nd contact with Ag	Ab mediated Type I,II &III	T cell mediated Type *IV*

Type IV (Delayed or CM) Hypersensitivity

Mechanism

Interaction of MQ & T cells

CD4+ recognize Ag with **MHC classII** on APC

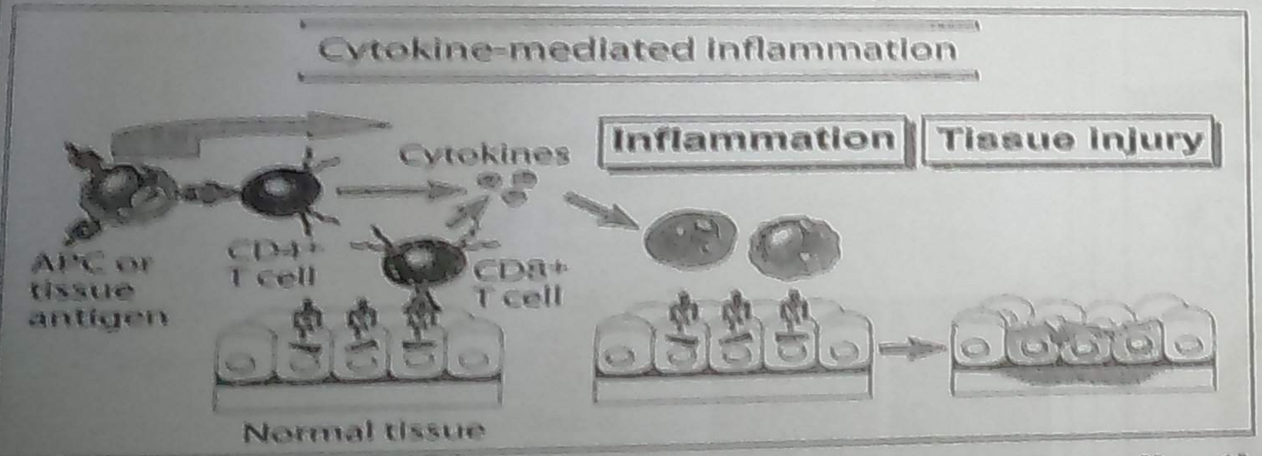
Release of **inflammatory cytokines** from **Th1&MQ**

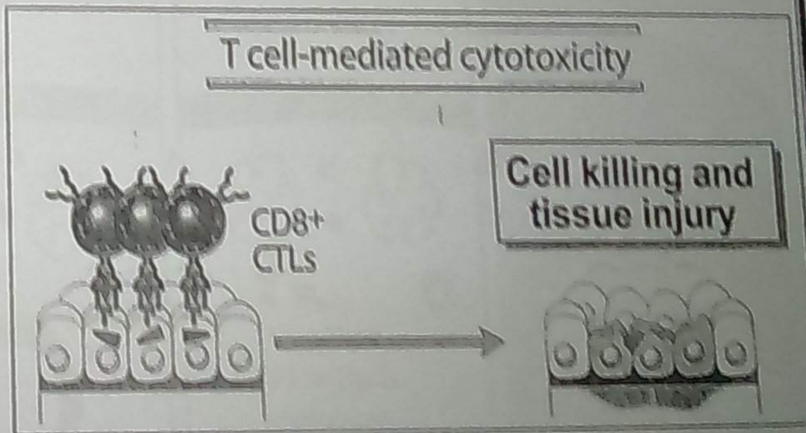
Recruitment of more lymphocytes & MQ

Inflammation & tissue damage

CD8+ (CTLs) attack cells

displaying Ag in association with ***MHC class I***





Clinical applications

28

Tuberculin test	Granulomatous ds	Contact dermatitis	DM	Acute & chronic graft rejection

Tuberculin test

Method & +ve result

ID injection of **PPD** (purified protein derivative)

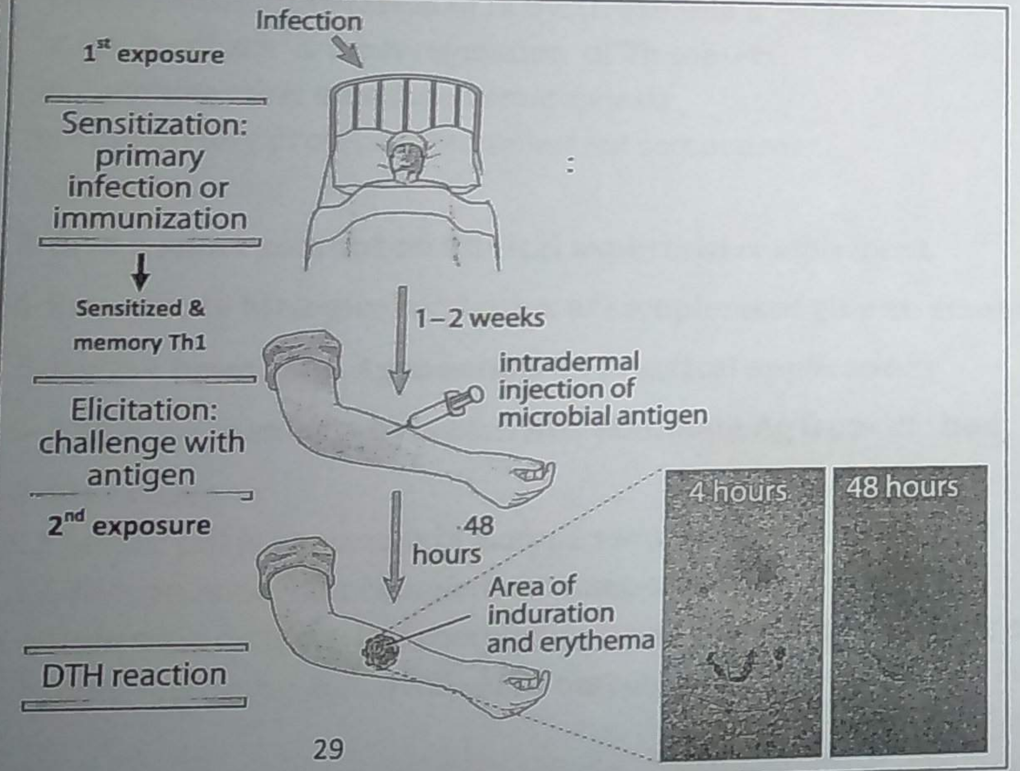
of **Mycobacterium TB**

↓ 48 hrs

Erythema & Induration

in a person previously exposed to TB bacilli due to:

- **Subclinical ds**
- **Clinical ds**
- **BCG vaccination**



Mechanism

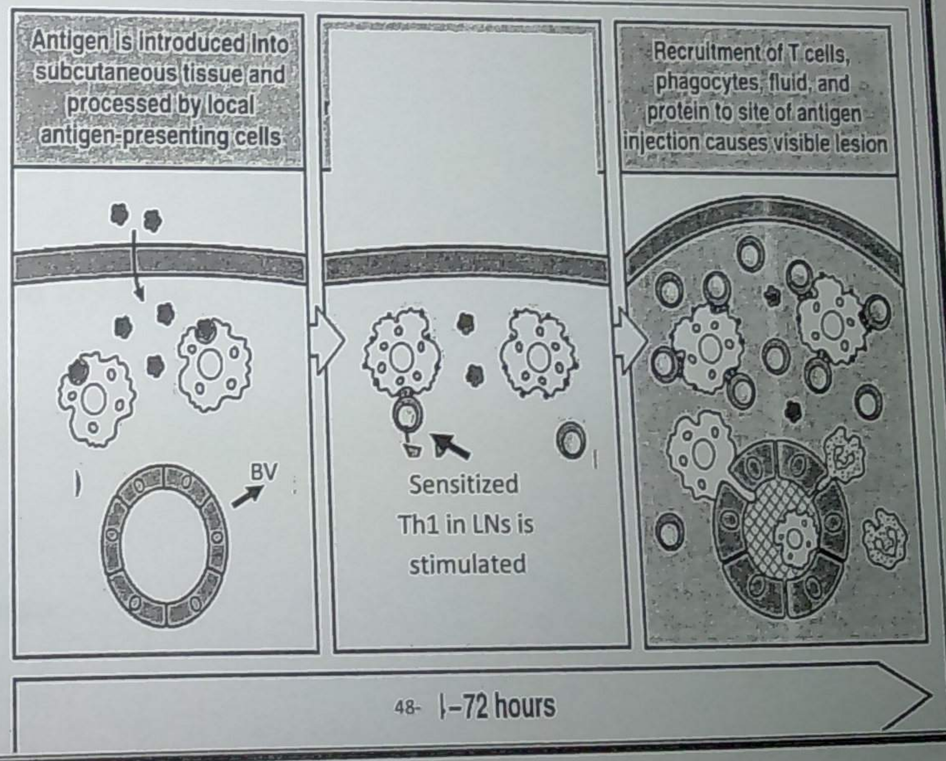
MQ & dendritic cells at site of injection uptake PPD

DCs migrate to LNs → **present Ag to sensitized Th1**

Sensitized Th1 migrate to site of Ag & secrete cytokines

Recruitment of more lymphocytes & MQ with VD

Induration & Erythema



Essay Questions

1-Compare &Contrast between:

i.T cell receptor & B cell receptor
ii.T cell dependent &T cell independent Ags.
iii.1ry & 2ry IR
iv.Opsonization & ADCC
v.The 3 pathways of complement activation
vi.IR to IC & EC pathogens.

2-Give an account on

i.Isotype switch
ii.Secretory component
iii.IL4
iv.Mechanisms of evasion of IR by EC bacteria & parasites
v.+ve feedback & cross regulation of Th subsets
vi. Cytokines that stimulate hematopoesis
vii. Regulatory proteins of complement components.
viii.Hapten

3-Give a short account on Clinical aspects of complement.

4-Enumerate biological activities of complement,give an account on 1 of them

5-Define heterophil Ag,mention its practical applications

6- Name mechanisms by which Abs eliminate Ag from the body

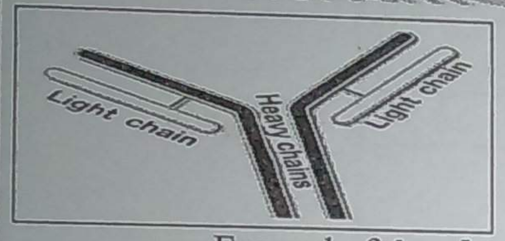
7-Give reason :

i.T helper cell is important in isotype switch of B cell
ii.C3b is an important complement component
iii.Inherited deficiency of complement may lead to angioneurotic edema
iv.Both interferon & IL 4 influence outcome of class switch.

Immunology 3

Humoral Immunity

Immunoglobulins (Ab)



Site

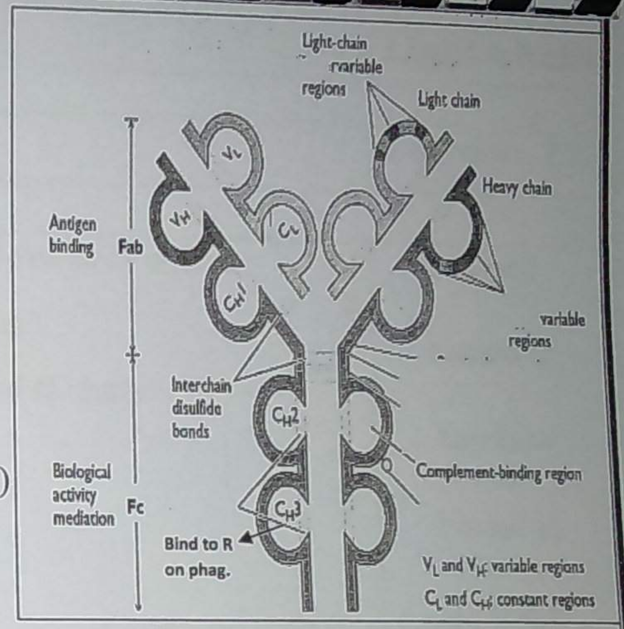
Glycoproteins found in all **body fluids (humors)**

Structure

Each Ab molecule is **Y shape**

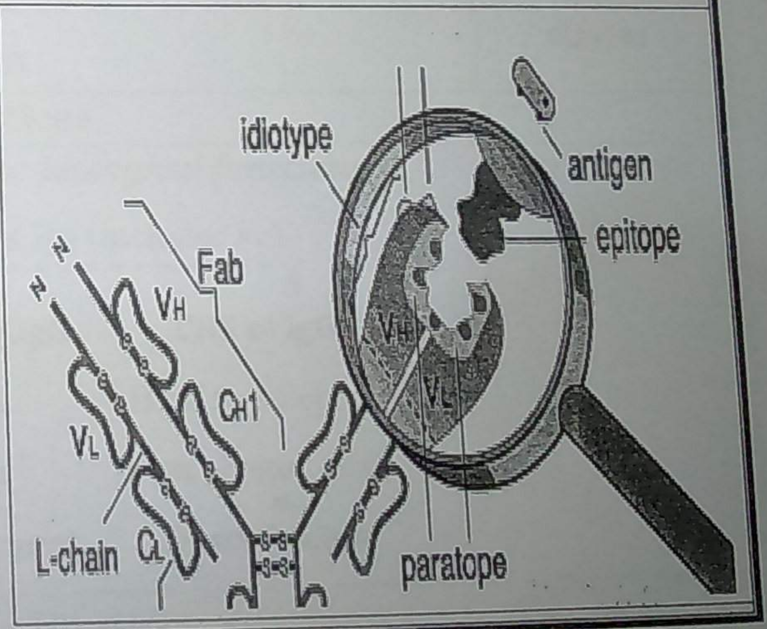
Formed of **4 polypeptide chains** connected by disulphide bonds

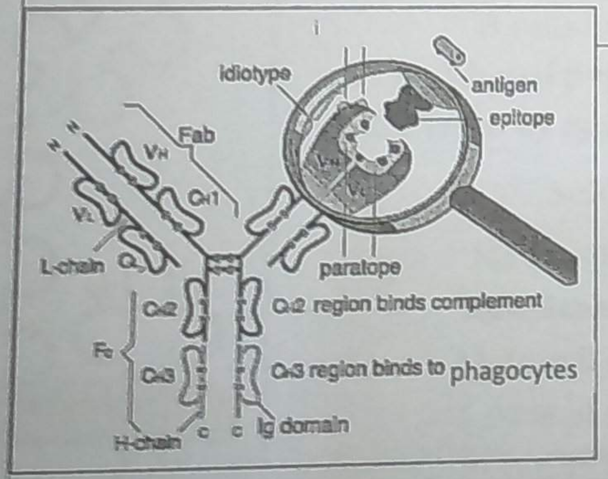
- *2 identical* ***heavy (H) chains***
- *2 identical* ***light (L) chains***
- ***Arranged in 3 fragments***
  - 2 Ag binding **(Fab)**
  - 1crystallizable **(Fc)**
- ***Each chain is formed of :***
  - **Variable** (V) region
  - **Constant** (C) region



Heavy and light chains

	Heavy (H) chain	Light (L) chains
I- Variable region	**A- Site**	
	Included in Fab	
	B-Structure	
	1 domain (VH)	**1** domain (VL)
	C- Functions	
	Forms the paratope or idiotype of Ab ⬇ Interacts specifically with **the epitope of Ag** (complementary to it) ⬇ Each idiotype is **unique** for 1 epitope & produced by a **specific clone** of B cell	



	Heavy chain	Light chain
II - Constant region	**A - Structure**	
	3 domains : CH1,CH2 &CH3	**1 domain** : CL
	B - Types	
	Change in a.a.sequence in CH region gives ***5 types*** of H chains ↓ Classify Igs into ***5 isotypes*** (classes) ↓ Each isotype is ***named*** according to ***type of H*** chain: 1- Gamma (γ) chain → Ig G 2-Alpha (α) chain → Ig A 3- Mu (μ) chain → Ig M 4-Epsilon (ε) chain → Ig E 5- Delta (δ) chain → Ig D	***2 types :*** **Kappa &** **Lambda** ↓ Found in all the **5 classes**
	C - Functions	
		Responsible for ***biological functions*** of different Igs (includes Fc) ↓ ↓ **CH2 of IgM&IgG**: Binding & activation ***of complement*** **CH3 of IgG**: Bind to receptors on phagocytes → ***Opsonization***	No functions

B lymphocytes

Functions

Responsible for **humoral IR** by producing Abs

↓

Eliminate **EC microbes & their toxins**

Professional APCs

↓

⊕Th cells

Origin & Maturation

BM (no need for thymus)

B cell receptor (BCR) complex

A-Structure & Diversity

Structure

BCR : surface (membrane bound) IgM&IgD

V (variable) region recognizes

specific epitope (complementary to it)

2 signaling mol.:Igα & Igβ

↓

Transmit **IC activation signal**

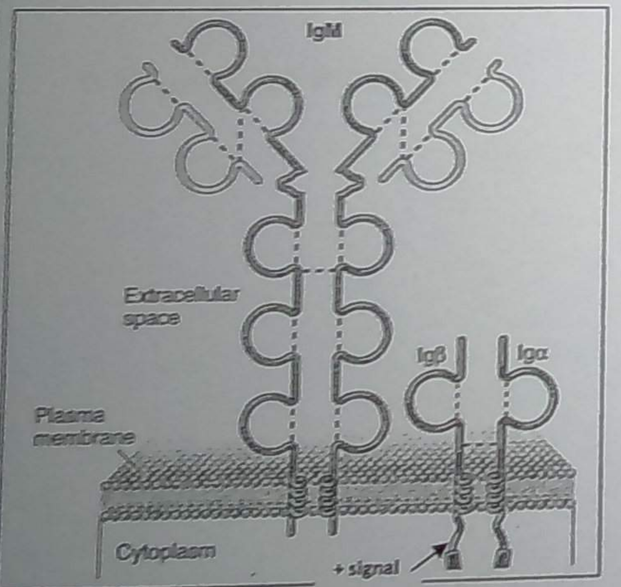
Diversity

Millions of B cells exist

↓

React with **millions**

of **different peptides**



B-Negative selection

B cells expressing BCR that can

react with **self peptides** (self reactive cells)

are killed by apoptosis *(clonal deletion)*

↓

Self tolerance

↓

No autoimmune reactions

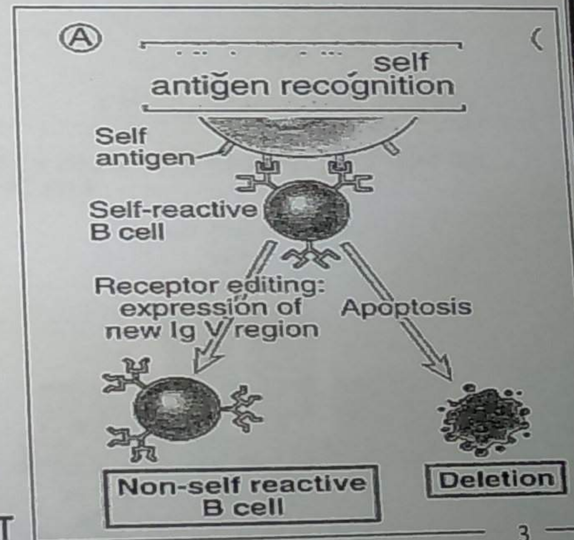
Release & Sites

Mature B cell circulate in blood

(***30 %*** of small lymphocytes)

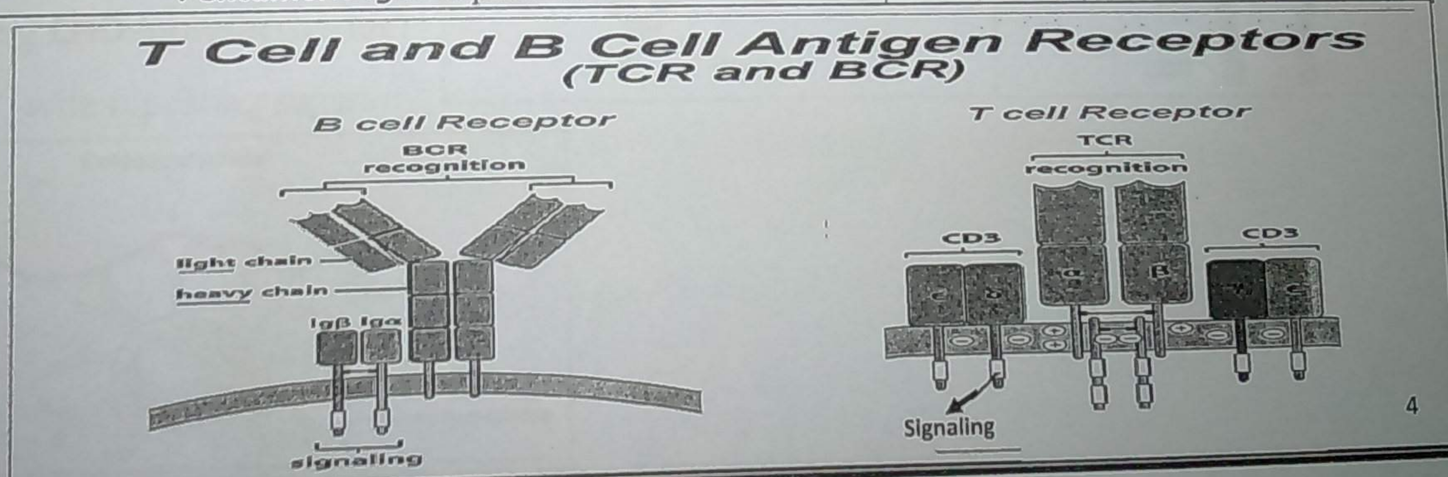
& the remaining are T Lymphocyte

2ry lymphoid organs : LNs, spleen & GALT



Comparison between B cell and T cell receptor

	B cell receptor	T cell receptor
1-Structure	*BCR complex* i.Membrane bound ***IgM & IgD***	TCR complex i.2 polypeptide chains: **α & β**
	ii.Signal transducing molecule	
	Ig α & Ig β	CD3
2-Ag recognition	By ***V regions of H & L chains*** of membrane bound Igs	By **V** regions of **α & β chains**
3-MHC restriction	***No*** Recognize Ag ***without MHC proteins***	Recognize Ag only **in association with MHC proteins**
4-Ag characters	***i.Free (soluble)*** **ii.Proteins** *iii.Lipids, polysaccharides, nucleic acids* *iv.Small chemicals e.g drugs*	**i.On APCs** **ii.Proteins**
5-Secreted form	***Yes*** ***Pentameric IgM*** is present in serum	**No** (always membrane bound)



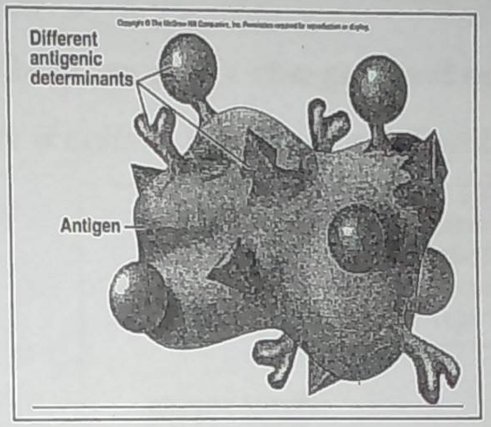
Epitope (antigenic determinant)

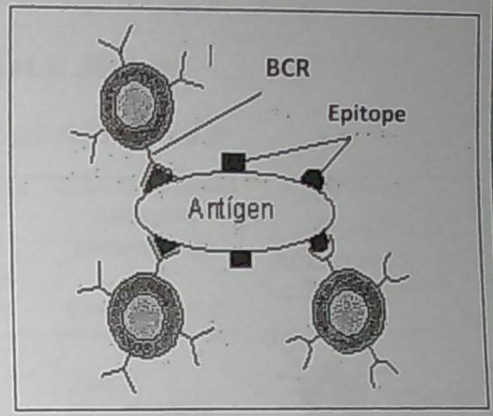
Size & Function

Is the **smallest biochemical unit** of Ag

that binds specifically with

- ***Ag R*** on B &T cells → ⊕ I R
- ***Paratope*** of secreted Ab

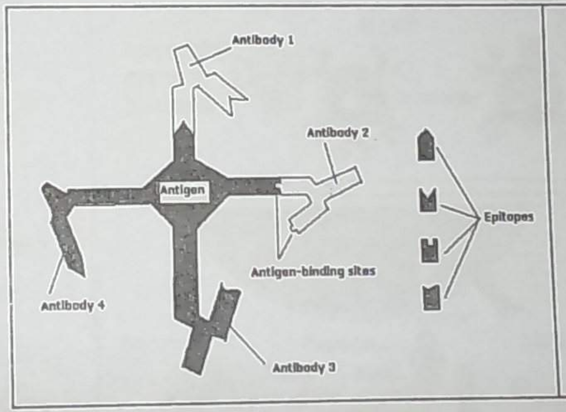


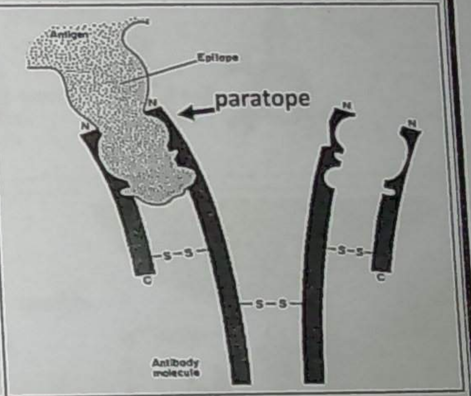


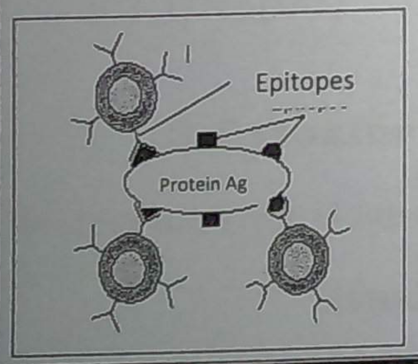
Types

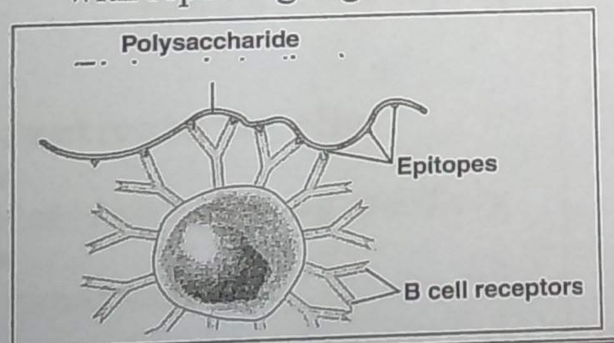
1 Ag may have

- Several ***different*** epitopes e.g **protein** Ag
- Several ***identical*** epitopes e.g **CHO (polysaccharide)** with repeating sugars









Activatio of B cells

I-Protein Ags: T (thymus) dependent Ags

Need ⬭ of T helper cells to activate B cells → B cells will act as APCs to Th

1-Ag binds to BCR (IgM & IgD)

⬇

Internalized (receptor mediated endocytosis)

⬇

Processed & associated with **MHC II proteins**

⬇

Displayed on the surface

2-Activation of Th cells

Peptide – MHC class II bind — B7 binds

TCR/CD3 complex & CD4 — *CD28(Costimulation)*

⬇

Cytokines production

IL2, IFNγ **(Th1)** ⟷ IL4, 13, 5, 6 & 10**(Th2)**

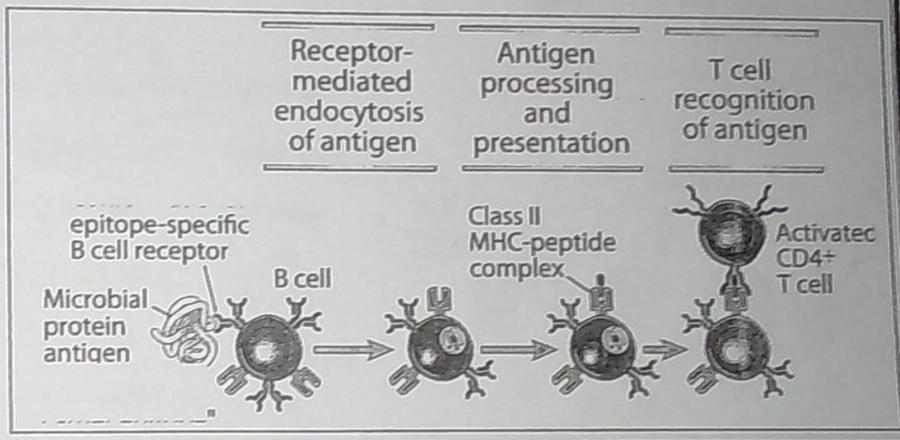
3-Cytokines activate B cells

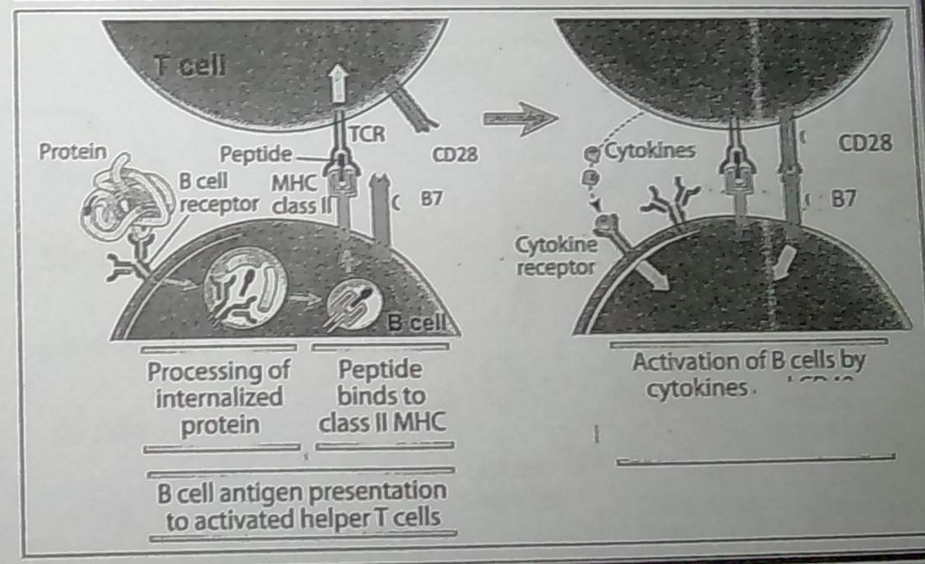
⬇

Proliferation into clone of cells with *same Ag specificity*

⬇

Clonal expansion





4-Differentiation of activated B cells into

A-Plasma cells

1-Effector functions

Produce thousands of Ab mol./ sec

specific

for epitope

Die after few days

2-Ab production

1st Produce **IgM** (secreted)

Isotype (class) switch

Is a change **in the H chain**

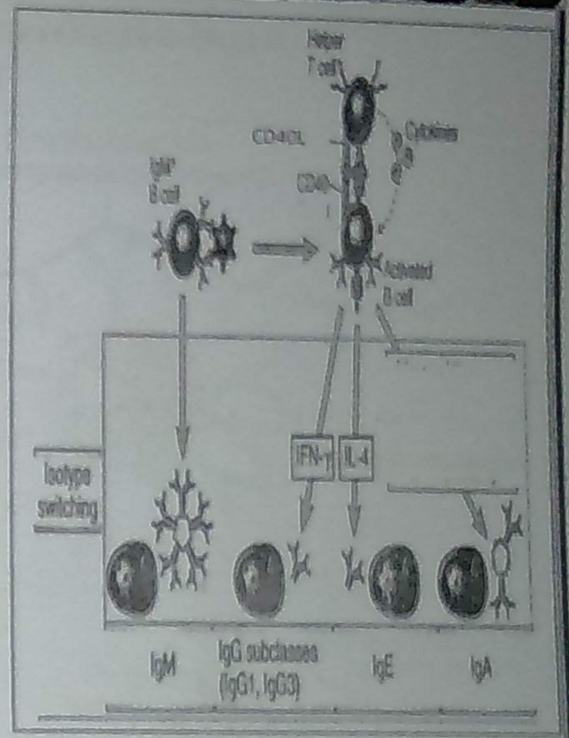
Production of another class of Ab while maintaining the same Ag specificity

Requires 2 signals

CD40 L on ⊕ ***T cells*** Binds to CD40 on B cells

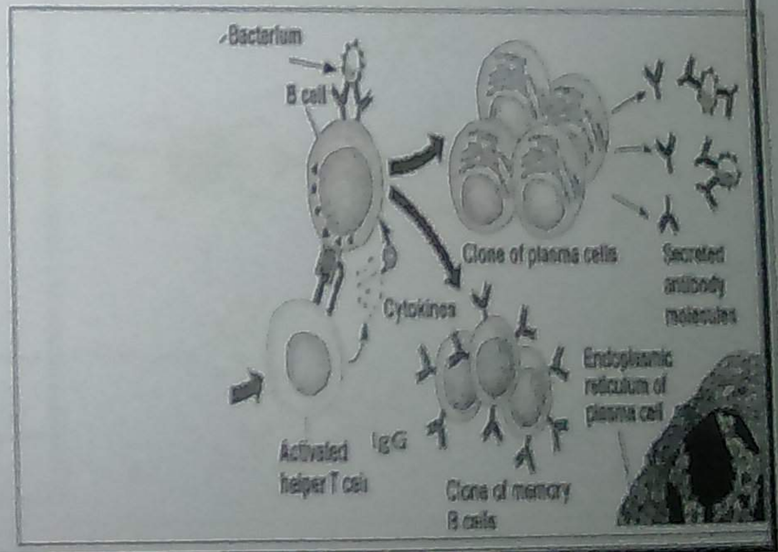
Cytokines

- ***IFNγ*** → IgG1&3
- ***IL4&13*** → IgE



B-Memory cells

Remain	**Express**	**Activated**	**Stimulated**	**Rapid &**
quiescent	surface IgG (Replaces IgM, D)	**rapidly**	**by**	**Strong**
for long	as	upon	cytokines	production
periods	Ag receptor	reexposure	from	of Abs
		to same Ag	memory Th	7



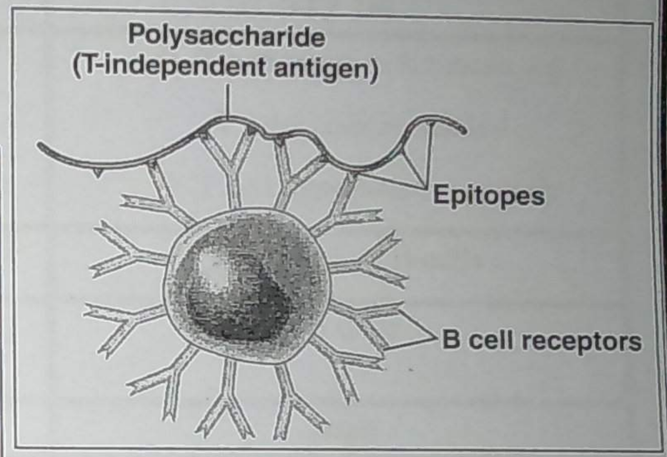
II-Polysaccharide Ags : T (Thymus) independent Ags

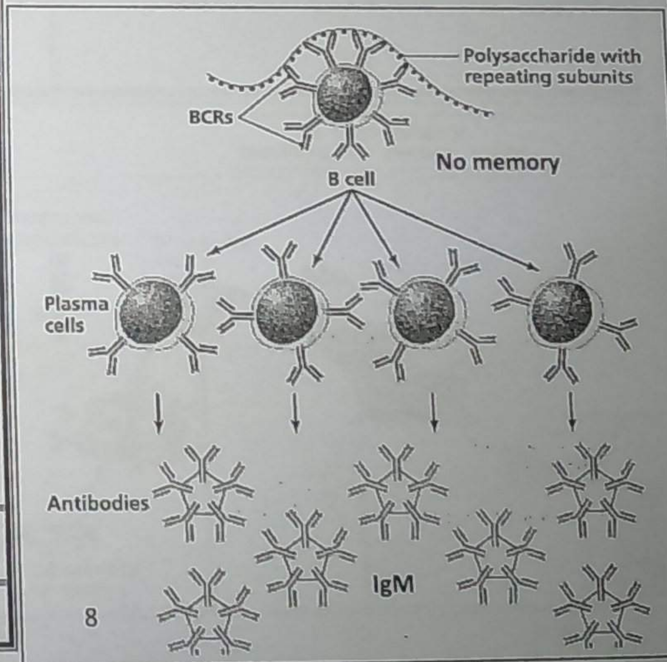
Activate B cells directly

⬇

No need for Th

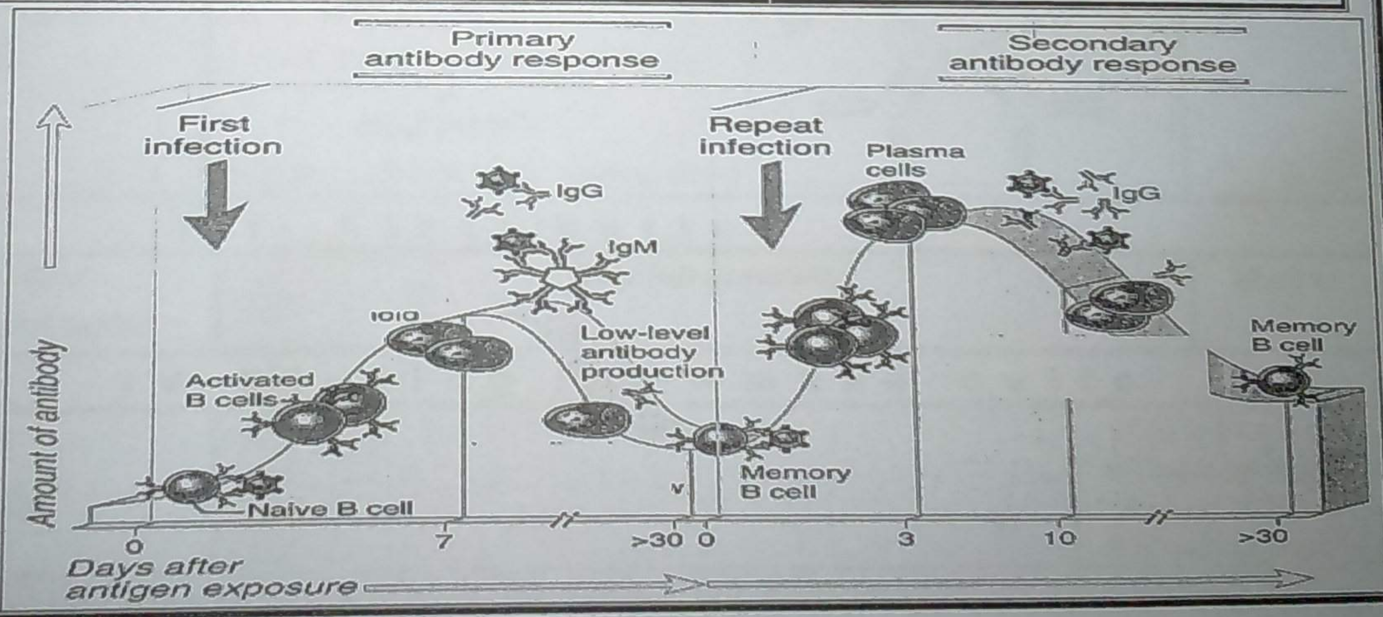
☆	T cell dependent Ags	T cell independent Ags
1- Structure & Examples	**Not formed** of repeating epitopes e.g • Proteins • Foreign RBCs • Hapten-carrier conjugate	Formed of *repeating multiple epitopes* e.g Bacterial **polysaccharides** (capsule)
2- Characters of IR	**i. Need ⊕ of Th cells** (B cell acts as APC)	*i.Activate B cells directly* faster response (No need for Th)
	ii.Isotypes of produced Abs	
	IgM + **IgG, A & E** (Isotype switch)	*IgM only* (*No isotype switch due to absence of :* IFN γ , IL4 &13)
	iii.Memory (anamnestic) response	
	Present	*No*





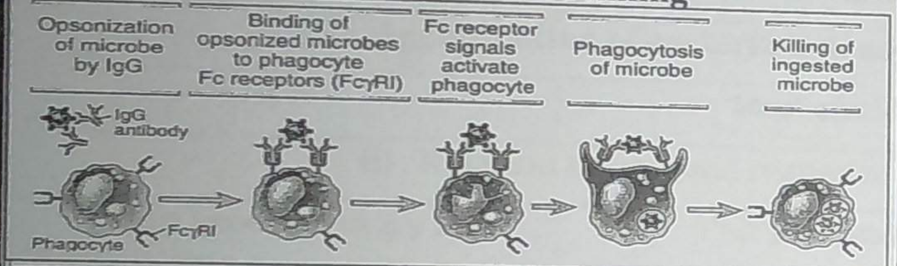
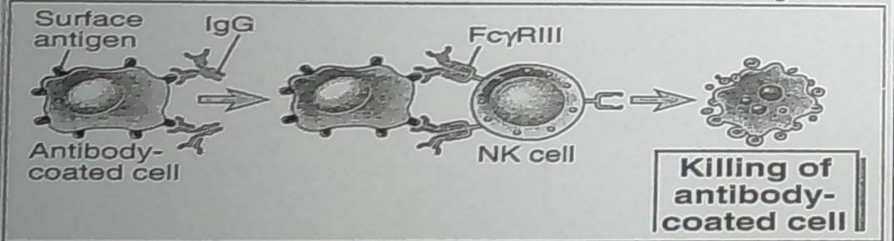
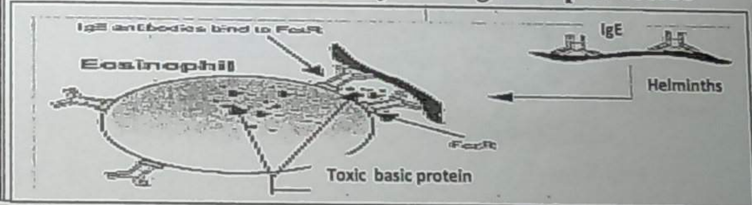
Comparison between 1ry & 2ry humoral IR

	1ry IR	2ry IR
1-Ag	✓ 1st exposure to Ag ✓ High conc.is needed ✓ T cell dependent & independent Ags	❖ *Reexposure* to the same Ag ❖ *Low conc.*is needed ❖ T cell *dependent* Ags *only*
2-Responding B cell	⊕ of naïve B cells	⊕ of *memory* B cells
3- Lag period following exposure to Ag	4-7 days	*1-3* days
4-Ab level	Low	*High*
5-Main isotype produced	IgM	*IgG*

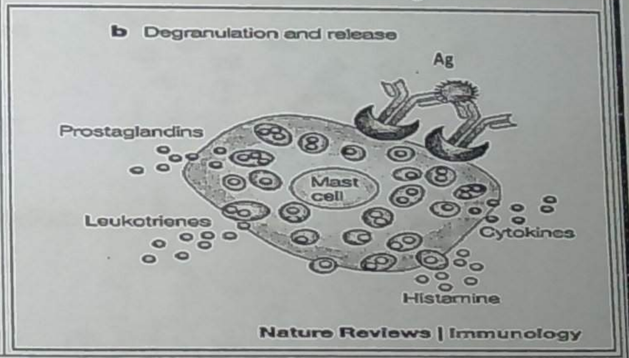


Ig Isotypes

IgG	IgM	IgE
I- Concentration (of total serum Igs)		
80% → most abundant	5-10%	Very low
II- Structure		
A- Heavy chain & subtypes		
1- γ chain **2- 4 subtypes → 4 subclasses:** i.IgG1: *predominant* ii.IgG2,3&4 (lowest)	1- μ chain (has an extra CH4) 2-No subtypes	1- ε chain 2-No subtypes
B- Molecular forms & MW		
Monomer → ***Lowest MW***	**1-Monomer** (membrane bound): BCR ***2-Pentamer*** (serum form): 5 monomer joined by **i. Disulfide** bonds **ii. J chain** : Links 2 of the Fc ↓ ***Highest MW*** (Highest valency:10 Ag binding sites)	Monomer
III- Distribution		
Diffuse ***easily extravascular*** ↓ Neutralize viruses & bacterial toxins	***Only Intravascular***	***Mucosa***
IV- Binding to immune cells		
Binds to **Fc γ R** on phagocytes &NK cells	No	Bind to **Fc ε R** on: i.Tissue mast cells &blood basophils ii.Blood eosinophils

IgG	IgM	IgE
V - Functions		
1-Opsonization (enhancement of phagocytosis)		
IgG1& G3 *(or C3b)* coat organism ↓ Bind to Fcγ R (or **C3bR**) on phagocytes (MQ&neutrophils) ↓ Facilitate ingestion: IC killing 	NO	
2-ADCC (Ab dependent cellular cytotoxicity)		
Ig G1&G3 coat *target cells: VIC or tumor cell* ↓ Bind to Fcγ R on *NK* or phagocytes ↓ *Release* of granular toxic mediators: *EC killing* 	NO	IgE coating **helminths** binds to FcεR on **eosinophils** ↓ Degranulation & release of *toxic basic protein* ↓ EC killing of worm ***IgE** is the main **host defense** against **parasites*** 
3 - Complement activation : by classical pathway		
♣ *G3 : Most potent* ♦ G1&G2	Most efficient	NO
4-Neutralization		
IgG binds to viruses, EC bacteria &toxins ↓ **Prevent** their **binding** to **target** cell	NO	

IgG	IgM	IgE
5 - Other functions		
i . Placental passage		
Only Ig (except G2) that crosses the placenta ↓ **Immunity to fetus & neonate**	No,but is the 1st Ig synthesized by fetus ↓ Indicate **intrauterine infection** if ↑ in neonates	No
ii . Agglutination of bacteria &viruses		**ii.VD & inflammation in skin & mucosa of RT&GIT** Binds to FcεR on mast cells& basophils ↓ **Degranulation** on Ag binding ↓ Release of ***histamine*& *peroxidase***
Yes	**Most efficient** (HMW)	
iii . Relation to immune response		**iii.Type I hypersensitivity(allergy)** In case of excess IgE
Most important in **2ry IR**	1st & ***predominant*** in **1ry IR**	
iv - Membrane bound form		
Ag R on **memory B cells**	Ag R on ***mature*** **B cells** (but monomeric)	



Ig D

Concentration

0.2% of total serum Igs

Functions

Ag receptor (BCR) : Main membrane Bound Ig on mature B cells

IgA

I-Distribution &Concentration

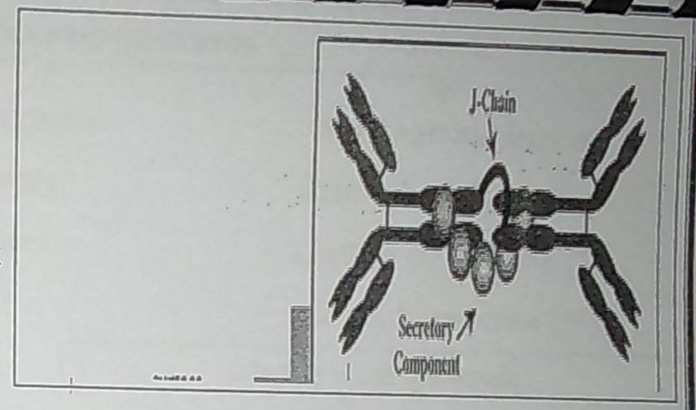
Serum IgA

10-15%
of total serum Ig

Secretory IgA

Main Ab in ***secretions***

♦ Saliva &tears ♦ Mucus of RT & GIT ♦ Breast milk



II-Structure

A-Heavy chain & subtypes

α chain

2- 2 subtypes → 2 subclasses:A1&2

A1 is inactivated by protease of
Neisseria , Pneumococci&H.influenza

A2 is more important in mucosal immunity

B-Molecular form of secretory IgA : Dimer

2 monomers joined by:

i.Disulphide bond

ii.J chain

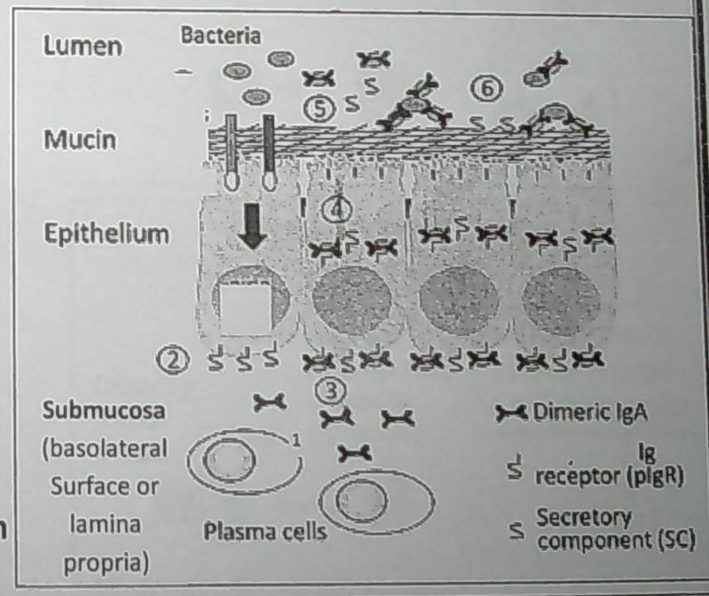
(synthesized by submucosal plasma cells)

Secretory (S) component

Produced by epethelial cells

i.Facilitates IgA transport across mucosa

ii.Protects IgA from digestion by proteolytic enzymes in secretions



III-Functions

Local mucosal immunity (gate keeper)

Coat bacteria &viruses in mucosa

Prevent their adherence(neutralization)

Prevent their entry into tissues

Present in colostrum & milk

Protects newborn from infection

Ab mediated effector functions

Opsonization

IgG (M)

ADCC

IgG (M) IgE (M)

Complement activation:

by classical pathway

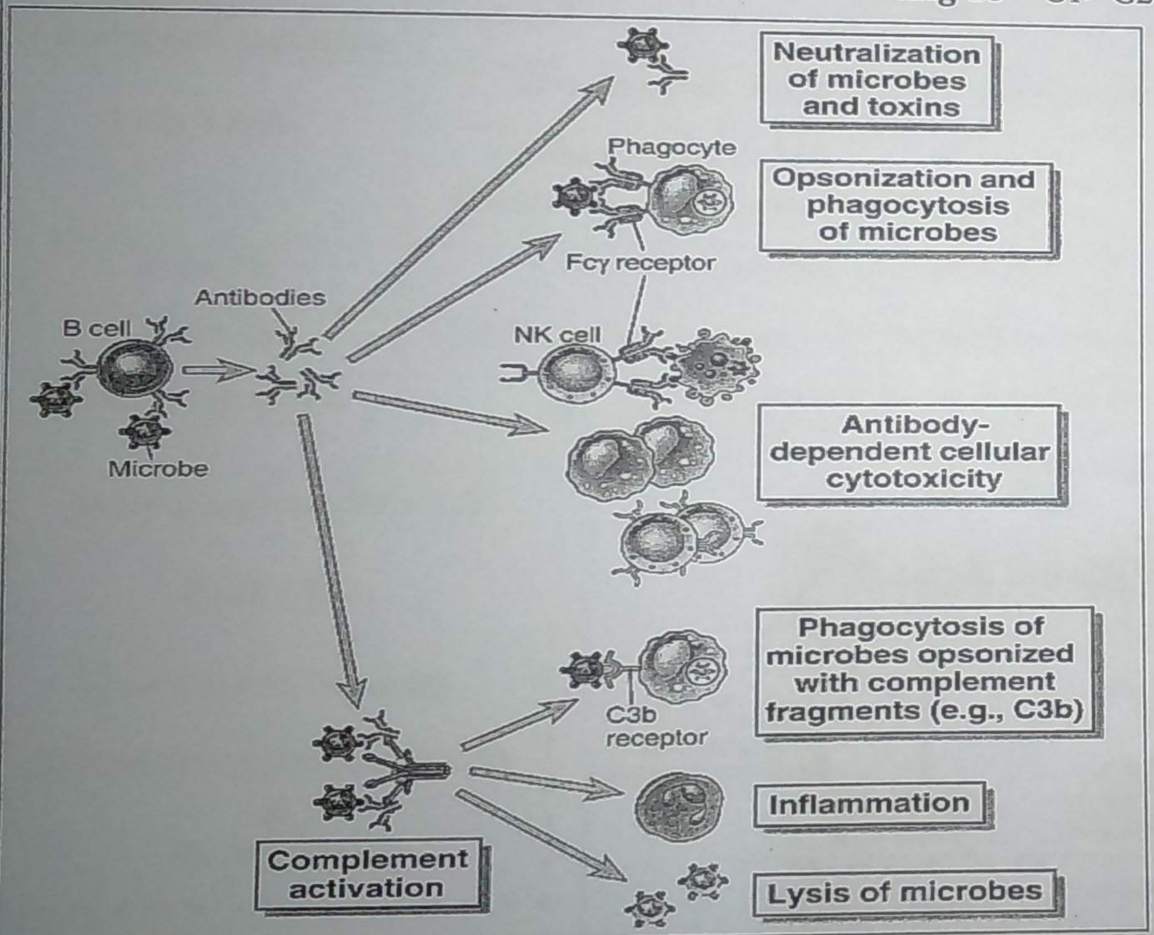
i. IgM *: most efficient*

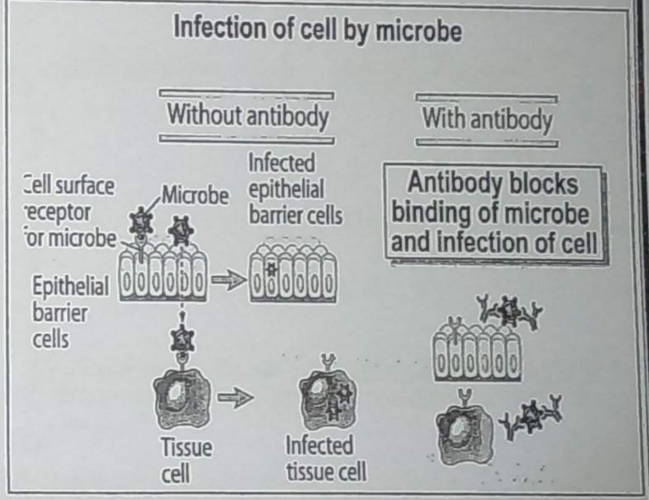
ii.Ig G3 > G1> G2

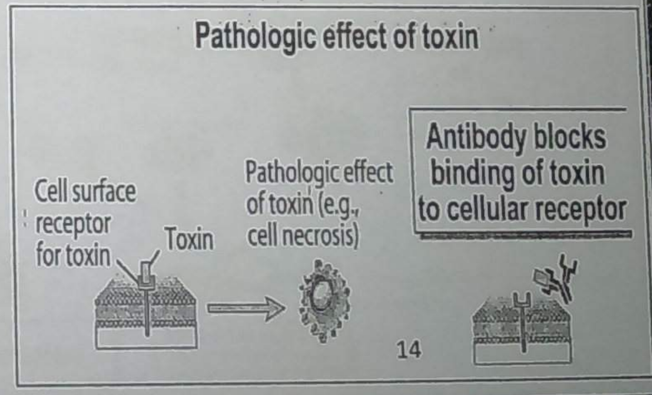
Neutralization of microbes & toxins

i.IgG:in circulation (M)

ii.IgA:in mucosa (M)







Cytokines regulatin (Adaptive immunity)

IL4	IL13	IL5
Main source : Th2		

	IL 4	IL 13	IL 5
A-Other sources	Mast cells		
		NK cells	
B-Biological functions			
1.On B cells	**i.Proliferation** of B cells → differentiation into **plasma cells** → **Ab** production		
	ii.Isotype switch to IgE **(Excess** may induce **type I** hypersensitivity)		
2-On Th	⊕ **differentiation of Th into Th2**		
3- b.On MQ	⊖ ***MQ activation*** → ⊖ ***Th1 formation*** → ***↓ IFNγ***		
C.Other functions		↑ mucus production by epithelial cells	⊕ ***eosinophils*** → kill helminthes (ADCC)

Other cytokines from Th2

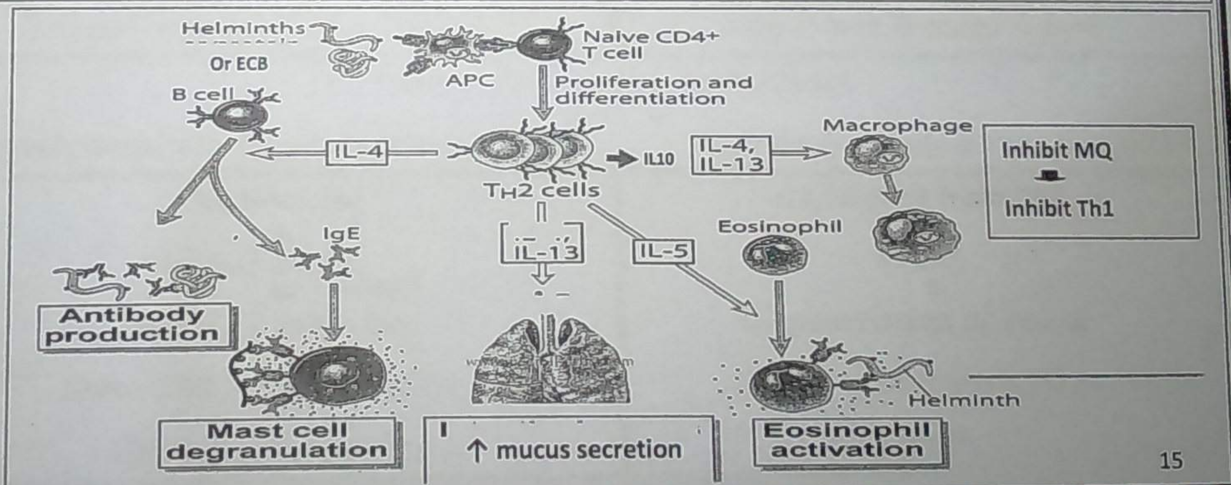
IL10 & IL6:

⊕ proliferation of B cells

differentiation into **plasma cells**

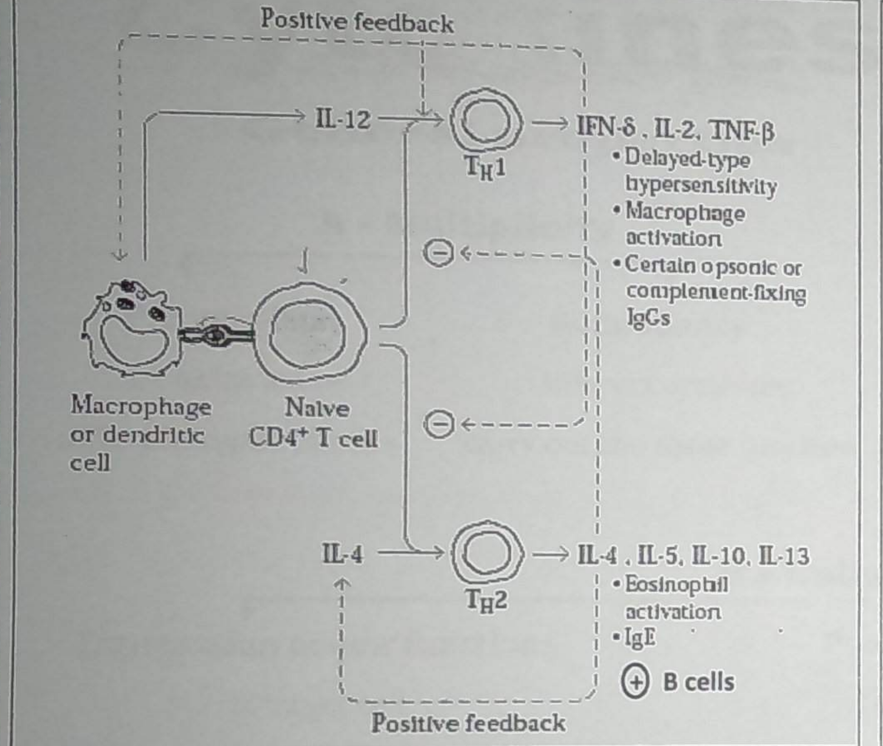
⬇

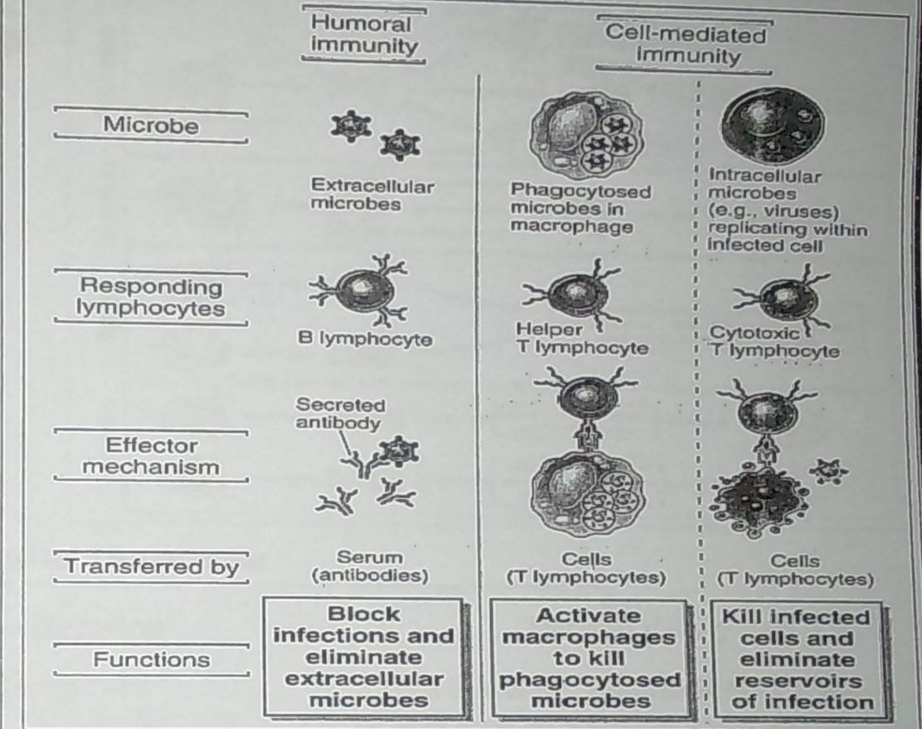
Ab production



Comparison between T helper 1 & T helper 2 cells

	Th1 cells	Th2 cells
1-Formation	By **IL12** secreted from **MQ & DCs**	By ***IL4*** secreted from ***mast cells***
2-Main role	Immunity against **IC** bacteria ,**viruses,fungi** & **tumor cells**	Immunity against ***EC*** bacteria , ***their toxins & parasites***
3-Cytokines production	**i.IL2, IFNγ and TNF α & β**	***i.IL 4,13,5,6 & 10***
	ii.IL3 & GM-CSFs	
4-Cytokines functions	**i. ⊕ MQ** to kill IC org.(IFNγ) **ii.↑ cytotoxicity of Tc & NK cells** (IL2) (natural Killer). **iii.↑ production of opsonins:IgG1&G3** (IFNγ) Coat org. ↓ Bind to Fcγ R on phagocytes ↓ Opsonization	***i⊕ eosinophils*** to kill helminthes (IL5) (ADCC) **ii.⊕ B cells** ↓ ↑Ab production & isotype switch to IgE (IL4&13)
5-Harmful effects	**Delayed hypersensitivity** (type IV)	***Anaphylaxis & atopy*** *(type I)*
6- +ve feed back & cross regulation	Cytokines produced by **each subset** **Positively regulate** the subset producing it ⟷ ***Negatively regulate*** the other subset	
	IFNγ from Th1 ↓ **⊕** MQ & DCs (Dendritic cells) ↓ More IL12 production ↓ **More Th1** (+ve feedback) & **⊖generation of Th2**	***IL4,10 & 13 from Th2*** ↓ **⊖**MQ ↓ ***⊖ generation of Th1 &*** ***IL4 ⊕ generation o*** *(+ve feedb*





Each clone of B cell is **specific to 1 Ag** (epitope)

↓

Produce only ***1 type of V region (1 idiotype)***

↓

Present at the upper part of

Its **membrane bound** Ab (Ag R)

Its **5 secreted** Ab classes (Ig MAGED)

IgM & IgG produced from ***same clone*** of **B** cells (against capsule of Staph.) are :

i.Common in ..variable.....

ii.Different in ..constant heavy

Ig G against capsule of Staph.& **IgG** against capsule of Strep. (from ***2 different B clones***) are :

i.Common in ...constant.....

ii. Different in ...variable.....

16'

Cytokines

General properties

A - Multiplicity

Pleotropism

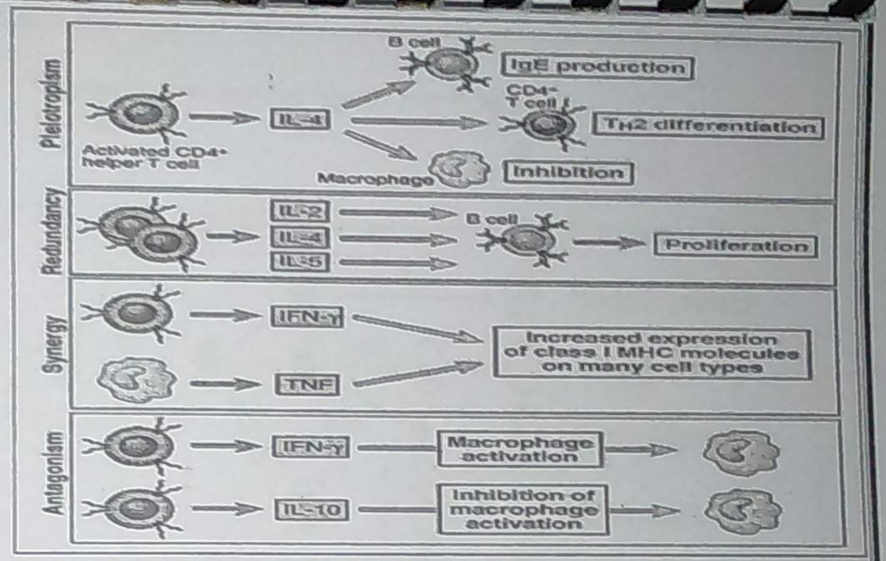
1 cytokine act on

different types of cells

Redundancy

Different cytokines

carry out the same function



B - Cellular response

Expresssion of new functions

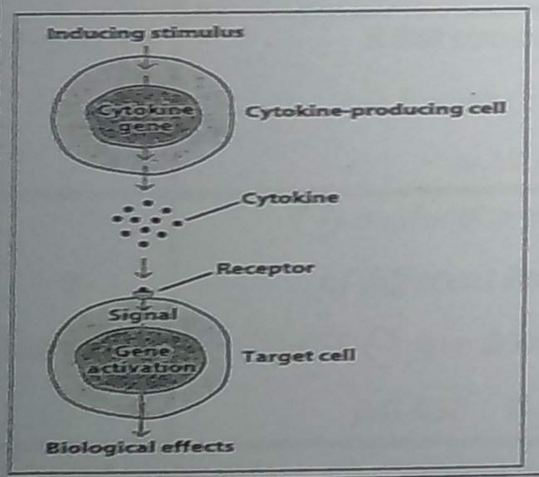
in target cell

Proliferation

of target cell

Turned down

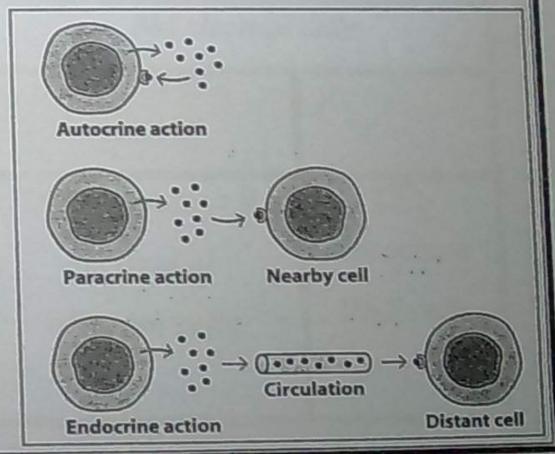
with **inhibitory feedback** mechanism



C - Actions (Not Ag specific)

They bind *to specific receptors* on

Cells of origin	Nearby cell	Distant cell
⬇	⬇	⬇
Autocrine	**Paracrine**	**Endocrine**



Functions

I-Regulators of innate immunity

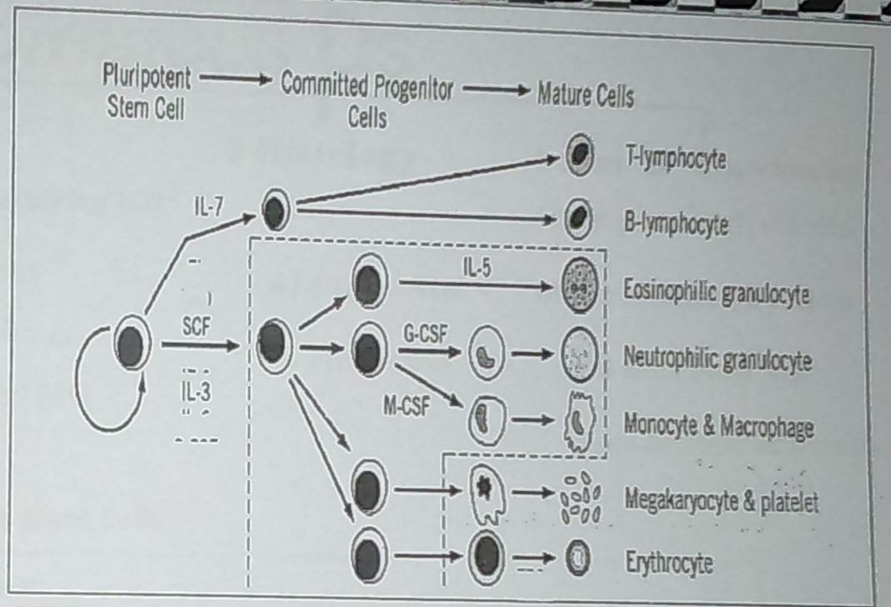
Inflammatory	Antiviral	Inhibitory
❖ TNFα,IL1,6&8	Type I IFN	IL10
❖ IL 12&18		

II-Regulators of adaptive immunity

IL2 , IFNγ & TNFβ	IL4, 5&13	TGF β

III-Cytokines with hematopoetic effect

⊕ growth & differentiation of **immature leukocytes**



	1-Colony stimulating factors(CSFs)	IL3	Stem cell factor	IL7
1-Source	i. Th1 & Th2			
	ii.BM stromal cells iii.Endothelial cells iv.MQ		*BM stromal cells*	
2-Functions	⊕ *production &↑ activity of different leukocytes* i.GM-CSF: ⊕ granulocytes&monocytes ii.G-CSF iii.M-CSF	*Support growth of all* ***hematopoetic precursors***	*Differentiation & survival of* ***all stem cells***	⊕ *immature* ***B&T cells***

Granulomatous Ds

1-Etiology

Infection

with ICB

e.g • TB

• Leprosy

2-Mechanism

Chronic antigenic ⊕ of MQ by surviving ICB

↓

Sensitization of Th cells

↓

Continuous release of cytokines

↓

Accumulation of **large n= of MQ**

↓

Release cytokines

↓

MQ fuse to form multinucleated giant cells

3-Histology

▲MQ

▲Lymphocytes

▲ Fibroblasts

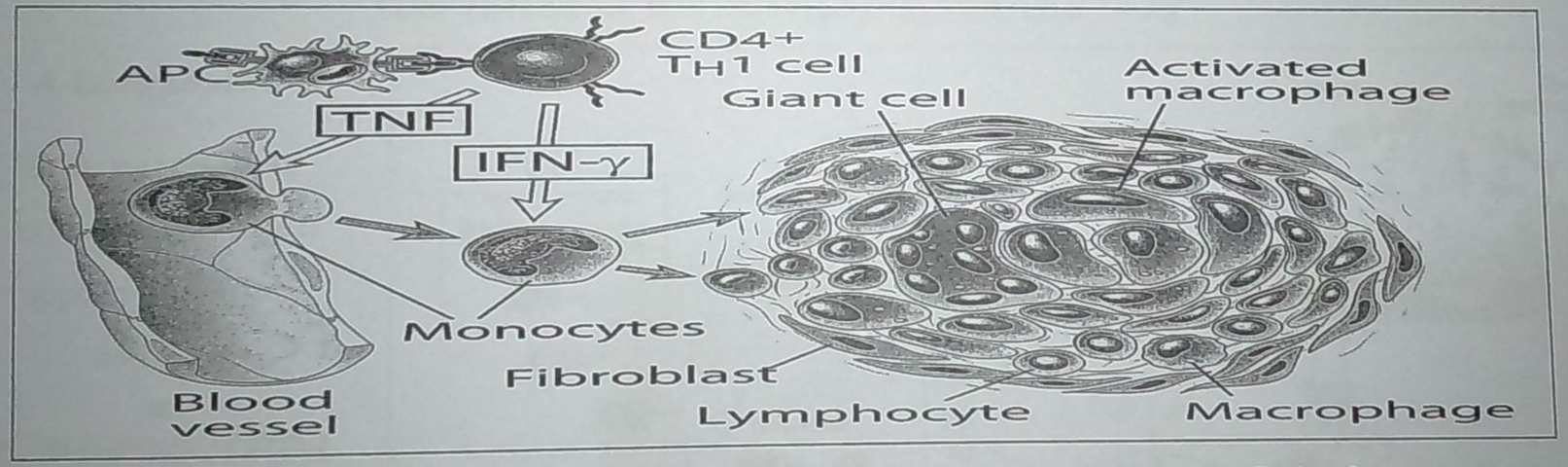
4-Aim & drawbacks

Attempt to wall off site

of persistent infection

but associated with

tissue necrosis & fibrosis



Autoimmune Ds : Insulin Dependent Diabetes

CTLs react against pancreatic cells damaging it → prevent insulin secretion

Contact Dermatitis

1-Etiology

Direct skin contact with ***haptens :***

- ♣ **Skin ointements.**
- ♣ Hair dyes, cosmetics.
- ♣ Soap, poison ivy.
- ♣ Nickel jewelry.

2-Mechanism

Haptens bind to skin proteins (carriers)

↓

New Ags

↓

Ags are presented by **Langerhans cells** (APCs)

in skin to **CD4+Th1 cells**

↓

Sensitization & recruitment to skin,

(together with MQ &CTLs)

↓

CD8+ cells attack skin cells expressing MHC class I + Ag

3-Histology & clinical appearance

Mononuclear infiltrate

(peak at 12-15 hrs)

↓

Redness , edema &

oozing eczema

4-Diagnosis :

Skin patch test

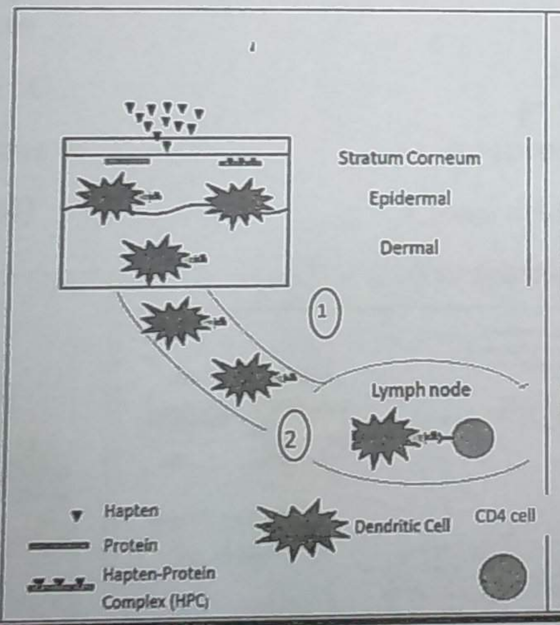
Suspected substance is applied to skin for

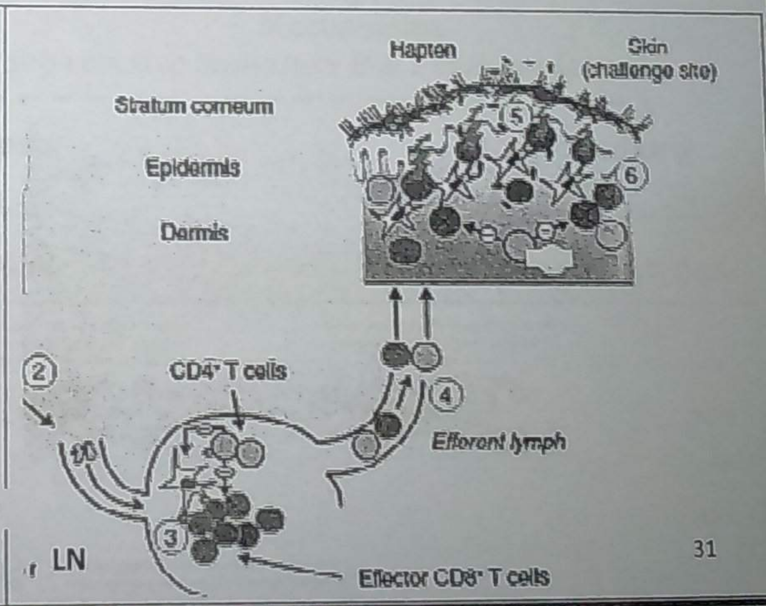
24-48 hrs

↓

Inflammatory eczema

at the site in +ve cases





Autoimmune diseases (AIDs)

Self tolerance	Etiology	Mechanisms of tissue damage	Laboratory diagnosis	Treatment

Definition

Adaptive IR attacking own body tissues

Self tolerance

Definition

Unresponsiveness to self Ags

Mechanisms

I- Central tolerance

Time

During *fetal life*

(Mainly)

Site

1ry LO

(Thymus & BM)

Mechanisms

Self reactive immature B & T cells undergo

Apoptosis

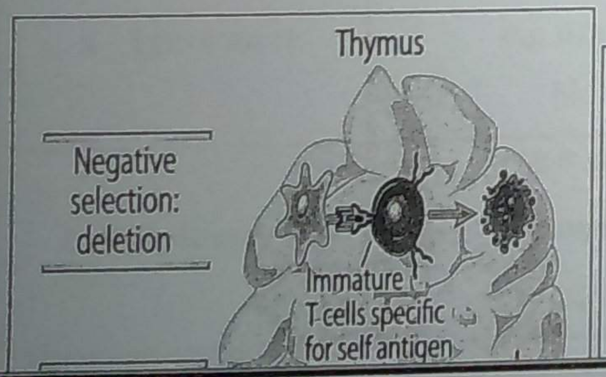
Clonal deletion

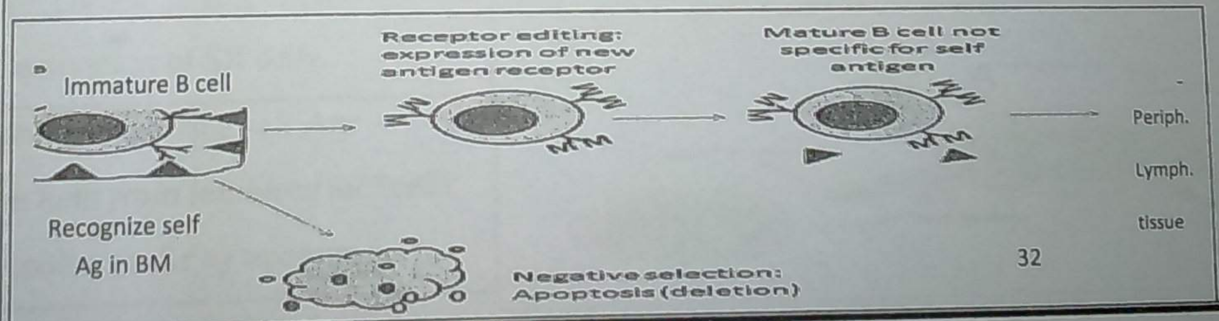
(-ve selection)

Receptor editing

Change receptors

stop recognizing self Ags

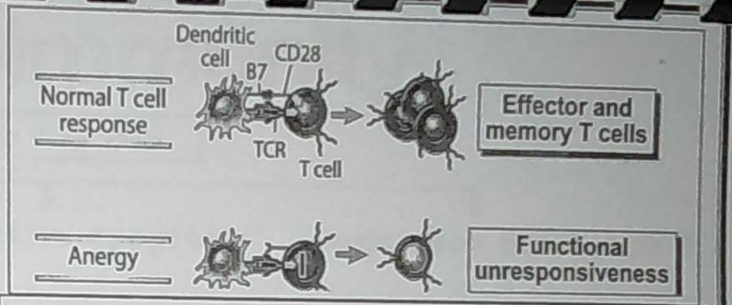


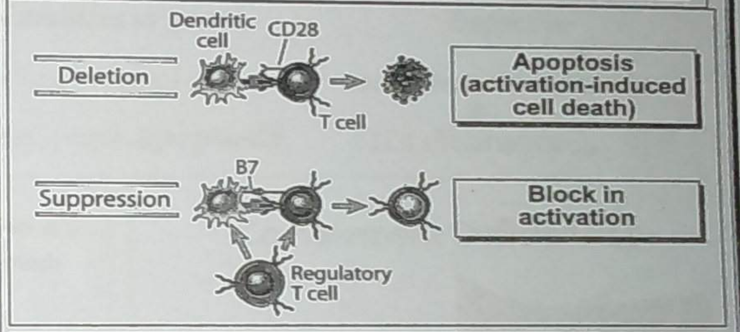


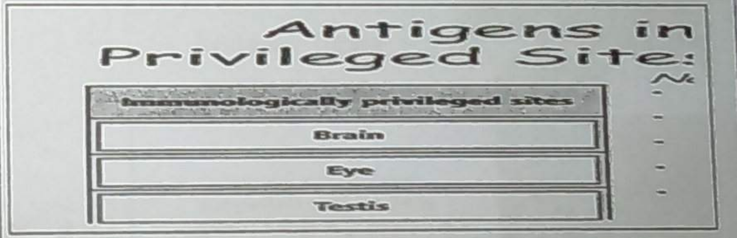
II - Peripheral tolerance

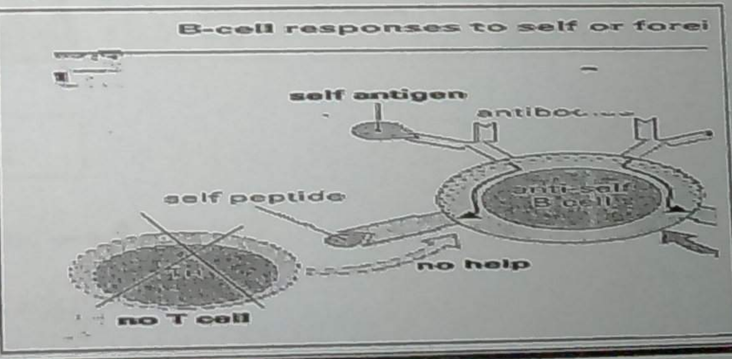
Time	Site	Mechanisms
Post natally	*2ry LO* (LNs& spleen)	⊖ *or deletion of SR mature T cells* escaping – ve selection

1-Anergy: Growth arrest	SR T cells receive antigenic signal ***without costimulation*** (No reaction between CD28&CD40L on T cells with B7 & CD40 on APCs) ⬇ Failure of proliferation& differentiation into effector cells
2 - Activation induced cell death	*Repeated⊕ of SR T cells by self Ags* ⬇ **Apoptosis** with deletion
3- ⊖by T reg cells	By **IL10 & TGFβ**
4 - Ignorance	*Sequestration of self Ags* e.g Brain,cornea, lens & sperms ⬇ No activation of SR cells
5-Helplessness	*SR B cells* recognizing self Ags ***don't receive help from inhibited SR Tcells*** ⬇ Unresponsive or die by apoptosis ٣









Etiology of autoimmunity

I-Genetic factors

Association with certain MHC genotypes

B27& ankylosing spondylitis ***DR4&rheumatoid arthritis***

♪Diseased persons may **not carry** these alleles &

these alleles may be **found in healthy** persons

Defective apoptosis

Abnormalities in genes

encoding proteins that

regulate lymph.**apoptosis**

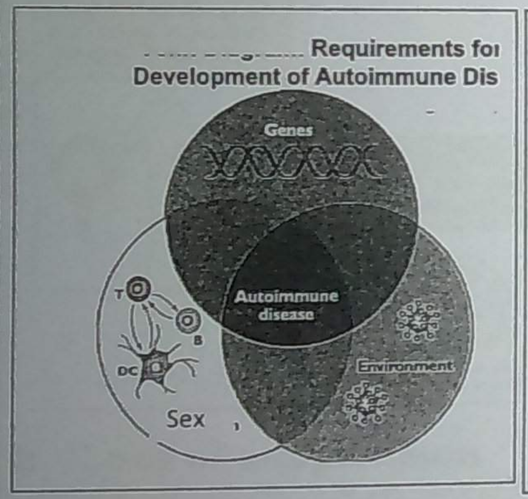
Deficiency in C1,4 or 3

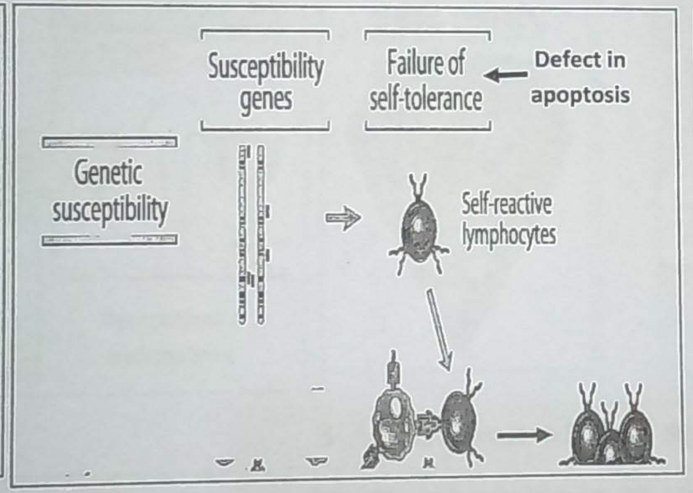
Defective

complement activation

↓

↓ ICs clearance → SLE





Complement Deficiencies

Systemic lupus erythematosis

- Deficiencies in the classical complement pathway renders pts more likely to develop immune complex diseases – SLE

II – Sex

↑ sex hormones in child bearing period → **↑AIDs in ♀**

e.g Grave's ds, SLE, multiple sclerosis

III - Environmental factors

1-Infections & Trauma

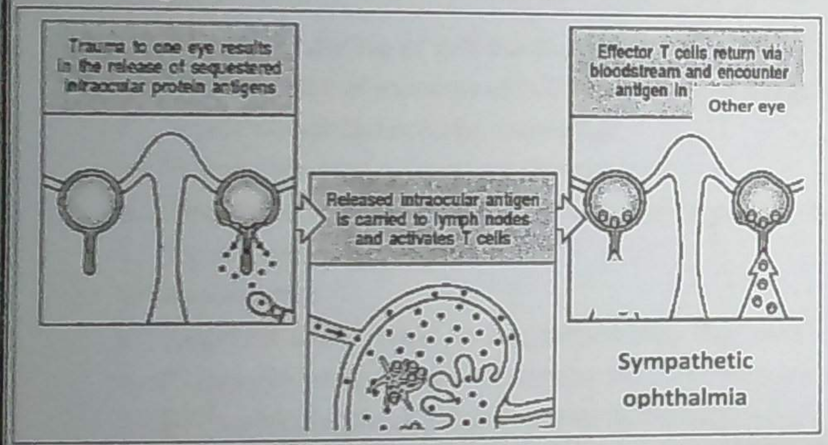
Trauma

Release of sequestered Ags

(brain,cornea,lens,sperms)

that haven't induced self tolerance

⊕ &recruitment SR T cells



Bacterial toxins

acting as superAgs

Polyclonal ⊕ of lymphocytes

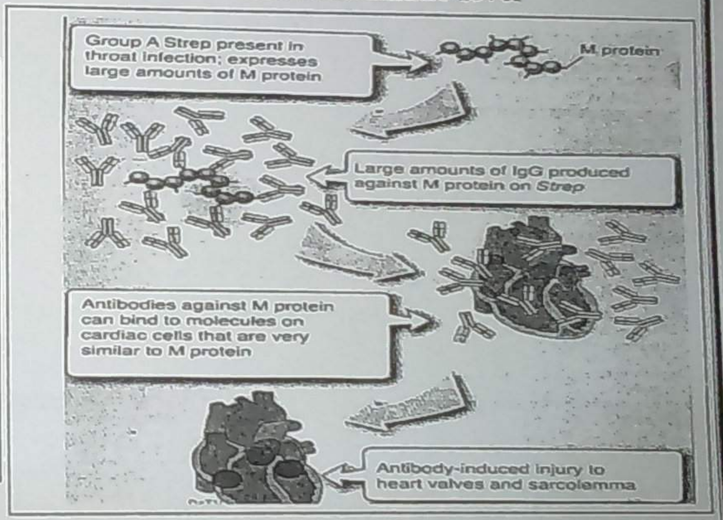
(including SR clones)

Molecular mimicry

Between Str.pyogenes Ags & heart myosin

Antistreptococcal heterophil Abs

cause rheumatic fever



2 - Loss of suppression

↓ n of T reg with age

Suppressed SR cells

become active

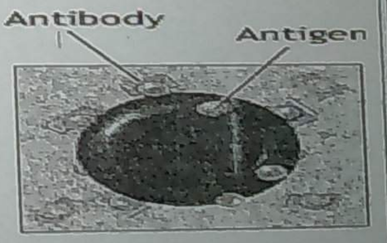
↑ AIDs in elderly

3-Alteration of self Ags by : drugs, chemicals or viral inf.

Drugs (haptens) coupling with RBCs

alter self Ags

AI hemolytic anemia



Essay questions

1- Compare & contrast :

a. +ve & -ve selection of Tcells.
b. MHC class I&II.
c. Killing mechanisms of MQ &CTLs.
d. Tc & NK cells
e. Naïve &memory T cells.

2- Give a short account on :

a. Importance of MHC mol. In health & disease.
b. Functions of APCs.
c. IL12.
d. Down regulation of cell mediated IR.
e. Mechanisms of evasion of ICB or viruses or fungi from IR.
f. Septic shock induced by superAgs
g. Tuberculin test or contact dermatitis.
h. Anergy and ignorance as mechanisms of peripheral tolerance.
i. T cell anergy.

3- Give reasons :

a. Negative selection is an important step that occurs during maturation of lymphocytes.
b. IC Ags are presented in different way in comparison to EC Ags.
c. B7 molecule plays a dual role in immunity.
d. Type I interferon is the most potent antiviral cytokine.
e. Central tolerance to self Ags.
f. Infection & trauma may be associated with autoimmune ds.

4- Define superAg , give mechanism of action & examples.

Immunology 4

Immunization

Immunization

Definition

Induction of protection against infection with pathogenic organisms by **artificial safe procedure**

Ways

	Active immunization : Vaccination	**Passive immunization**
1-Method	Using **killed or attenuated** microbe or **part of it** → host to produce Abs/ or immune-reactive cells	Using ***preformed components of IR:*** Abs or CTLs
2-Onset of protection	**Delayed :** appears after a lag period	***Immediate***
3-Duration of protection	**Long term** due to memory cell	***Short term***

Comparison between active & passive immunity

	Active immunity	**Passive immunity**
I-Acquisition		
A-Natural	**Infection** → Clinical, subclinical	***Transfer of maternal Abs*** → Transplacental: IgG; In colustrum & milk : sIgA
B-Artificial (immunization)	**Vaccination**	**Injection of preformed Abs or CTLs**
II-Onset & duration of protection	.....	.....
III-Type of protection	**i.Protective** immunity ii.Immunological **memory**	***i.Transient protection*** ***ii.Alleviation of preexisting ds***

Active immunization by vaccines

Definition of vaccines

Any preparation producing ***immunity to a ds***

By ⊕ the production of **Abs or cellular immunity**

Without causing **severe infections**

Strategies for developement of vaccines

I-Whole organisms vaccines

	Killed (inactivated) vaccines	**Live attenuated vaccines**
1-Idea	**Org.is killed (inactivated)** **No replication** → No disease **Maintaining epitopes on Ag**	***Org.is attenuated*** ↓ ***Transient replication*** in host cell ↓ Mimics natural infection but in ***mild*** form ↓ No disease
2-Method	**1-Heat** **2-Chemicals**: formaldehyde or alkylating agents	***1-Repeated subcultures*** under abnormal conditions ***2-Genetic engineering***
3-Administration	**Injection**	***Natural routes*** of infection: Oral or intranasal
4-Examples	**Salk** vaccine of polio	***Sabin*** vaccine of polio

Killed Vaccines	Live attenuated vaccines
5-Disadvantages	**5-Advantages**
i.Given by **injection**	i.Given *orally or intranasal*
ii.Inefficient IR	*ii.Efficient IR*
a- Humoral	
Induce **systemic (IgG),** but not local (sIgA) immunity	Induce both *systemic(IgG)* & *local (sIgA)* immunity
b- Cell mediated	
Weak	***Strong***
c-Duration	
Short No multiplication in body → not similar to natural ds	***Long lasting*** *Multiplication* of atten.org.in *body* → *similar* to natural ds
iii.Herd immunity : Unimmunized individuals are indirectly protected by surrounding immunized individuals	
No	***Yes*** Live atten.strains are transmitted to other community members by **fecooral route**
iv.Failure to kill the org. ⟶ ds	
6-Advantages	**6-Disadvantages**
a.Stable : don't need cold storage	*a.Low stability*: need cold storage
b.Safe : no contraindications	*b.Safety problems of attenuated strains* **i.Serious illness in IS pts or during pregnancy** (fetal damage) **ii.Insufficient attenuation** Induce same complications as those seen in natural ds e.g Measles vaccine causes **encephalitis** in small % of recipients **iii.Reversion to virulence ⟶ ds**

II-Vaccines containing a portion of organism e.g capsule

Advantages

Avoid toxicity &

risk of infection

due to retained virulence

Disadvantages

Polysaccharide capsules are

thymus independent Ags

Conjugated to carrier protein

to become more immunogenic

Examples

Capsule&conjugated vaccine of:

i.Strept.pneumoniae

ii.Meningococci

III-Synthetic polypeptide vaccine

Preparation

Synthetic polypeptide *similar in its a.a sequence*

to viral or bacterial Ag

Used as vaccine

Disadvantage

Weak immunogen

IV-Inactivated toxins : toxoid

Preparation

Bacterial toxins are **inactivated (modified) by formaldehyde**

Toxoid : Non toxic,but immunogenic

Induce antitoxins that neutralize toxins

Uses

To prevent infection caused by

exotoxin producing bacteria

e.g C.diphtheria & Clostridia tetani

IV-Anti-idiotype Ab vaccine

Preparation

Idiotype (a.a.sequence in Ag binding site of Ab)

is injected into animal

⬇

Production of ***anti-idiotype***

(Abs to idiotype)

that ***mimics*** *part of*

the ***3 dimensional structure***

of its specific Ag

⬇

Used instead of it as vaccine

⬇

Induce an IR against infectious ds

e.g herpes,hepatitis B,polio &rabies

Value

When the original Ag

isn't suitable

e.g

i.Polysaccharide

ii.Lipid A bacterial toxin

Advantage

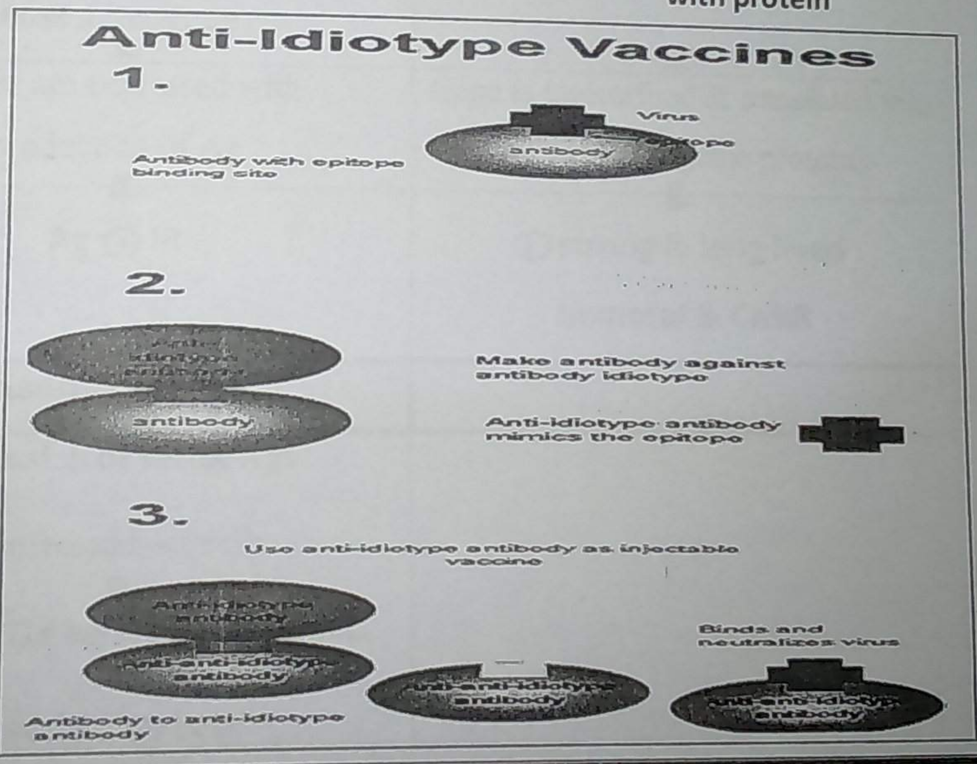
Induce memory

which polysaccharide

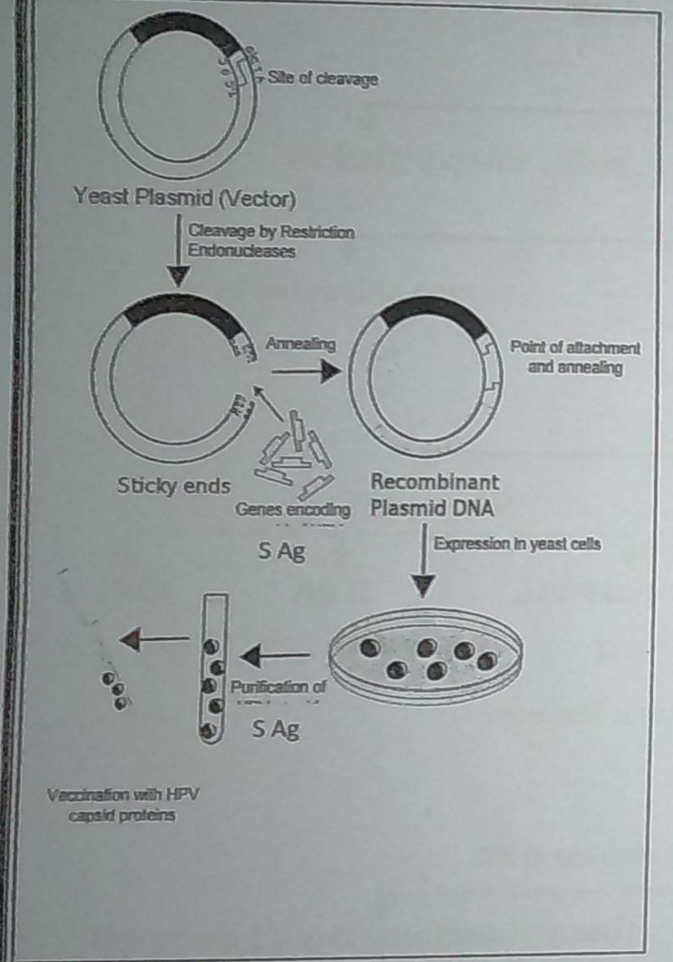
&lipid don't induce

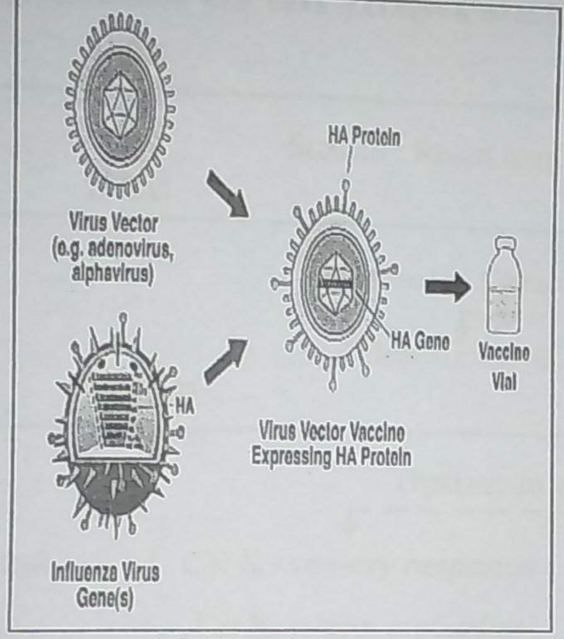
unless **conjugated**

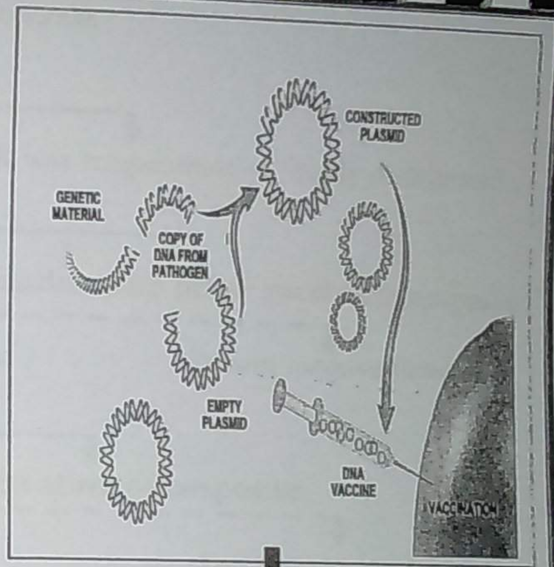
with protein

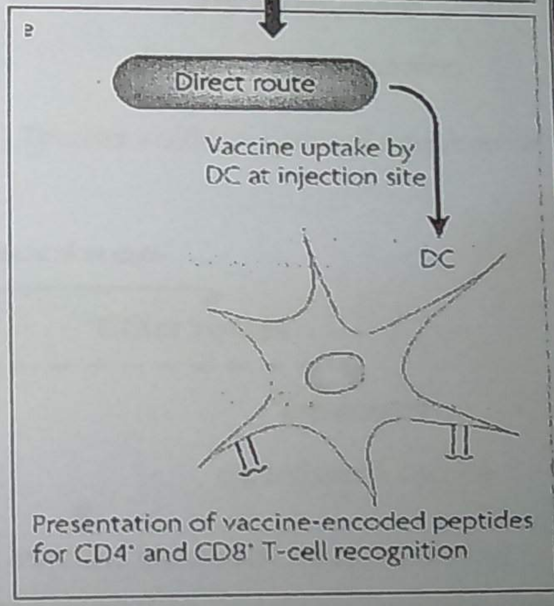


VI-Recombinant vaccines	VII-Recombinant vector vaccines	VIII-DNA vaccine
Gene encoding the most antigenic part in a microbe is identified	**Gene encoding major Ag** of virulent pathogen is identified	**Plasmid containing gene encoding major Ag** is injected in the body
↓ Inserted into vector **:plasmid**	↓ **Introduced into vector : attenuated bacteria or virus** e.g vaccinia virus	↓ ***Tranfects APCs (dendritic cells)***
↓ Recombinant plasmid is inserted into ***E.coli or yeast***	↓ Attenuated org.is injected into ***host*** to replicate	↓ Gene is transcribed & translated into Ag (immunogenic protein)
↓ Genes are expressed with production of Ag	↓ Genes are expressed with production of Ag	↓ ⊕ **strong & long lived humoral & CMIR**
↓ **Ags are purified & used as vaccine**	↓ **Ag ⊕ IR**	
	Disadvantages	
	Expression of vector Ags on infected host cells ↓ ***Killed by CTLs before vector replic.*** ↓ Vaccination fails	


Site of cleavage
Yeast Plasmid (Vector)
Cleavage by Restriction Endonucleases
Annealing
Point of attachment and annealing
Sticky ends
Genes encoding S Ag
Recombinant Plasmid DNA
Expression in yeast cells
Purification of S Ag
Vaccination with HPV capsid proteins


HA Protein
Virus Vector (e.g. adenovirus, alphavirus)
HA Gene
Vaccine Vial
HA
Virus Vector Vaccine Expressing HA Protein
Influenza Virus Gene(s)


CONSTRUCTED PLASMID
GENETIC MATERIAL
COPY OF DNA FROM PATHOGEN
EMPTY PLASMID
DNA VACCINE
VACCINATION


Direct route
Vaccine uptake by DC at injection site
DC
Presentation of vaccine-encoded peptides for CD4+ and CD8+ T-cell recognition

Properties of an ideal vaccine

1-2S

- **Safe** :no side effects
- **Stable** : Resist high & low temperature → easily distributed

2-2C

- Reasonable **cost**
- Administered in **Combination with other vaccine** to decrease
  - Health care visits
  - Person inconvenience

3-POD

- **Proper IR**
  - ***CMR*** — For ICB
  - ***Ab R*** — For ECB
  - ***Secretory IgA*** — For mucosal immunity
- **Optimum duration of response**
  - ***CM & memory response*** — For long term protection ⬇ **Resident** children receive .....
  - ***1ry Ab response*** — For short term protection ⬇ **Tourists** visiting a diseased area receive .....

Routes for administration of vaccines

- **Injection (most commonly used)**
  - ***IM & SC*** ***(most often)***
  - ID (IC)
- **Other routes**
  - ***Oral*** — e.g oral polio vaccine (Sabin)
  - ***Intranasal*** — e.g Influenza vaccine

⬇

local (mucosal) IR → mimics response induced by natural infection

Adjuvants

I-Definition

Substances that **non specifically enhance IR** against a certain Ag when mixed & injected with it

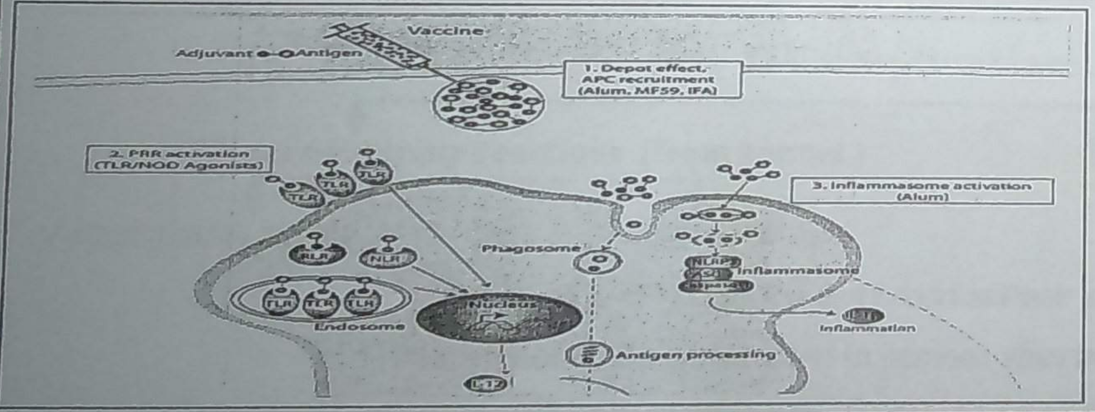
II-Characters

Chemically **irrelevant to Igen**

Induce **effective Ab (humoral) response**, but a weak CM response

III-Mechanism of action & Examples

i.↑ local inflammation	ii.Slow release of Ags	iii.↑costimulatory signals	Generalised ⊕ of immune cells
Influx of more **APCs** &↑**cytokines** production ↓ ***↑T&B cell response***	Prolongation of Ag persistence **(depot)**		***Cytokines: IL2,12,IFNγ,&GM-CSFs*** added to vaccines
Aluminium hydroxide added to Diphtheria &Tetanus toxoid			



Passive Immunization

I-Passive transfer of Igs

A-Source

Human or bovine

B-Indications

- **Post exposure prevention**
  - e.g rabies,HAV&HBV
- **Alleviation of existing ds**
- **Underlying illness**
  - preventing administration of vaccine

C-Types

- **Specific against certain ds**
  - ***Hepatitis A&B***
  - ***Antitoxins for***
    - ♦Botulism ♦Tetanus ♦ Gas gangrene ♦Diphtheria
- **Non specific**
  - ***Pooled Igs***
    - ttt of immunodeficiency

D-Complications

- **Hypersensitivity reactions (from animal)**
  - Anaphylactic shock
  - Serum sickness
- **Transfusion transmitted infections**

II-Passive transfer of CMI

Transfer of **CTLs** is restricted to persons ***sharing MHC class I genes***

Essay Questions

1-Compare &Contrast between:

i.T cell receptor & B cell receptor
ii.T cell dependent &T cell independent Ags.
iii.1ry & 2ry IR
iv.Opsonization & ADCC
v.The 3 pathways of complement activation
vi.IR to IC & EC pathogens.

2-Give an account on

i.Isotype switch
ii.Secretory component
iii.IL4
iv.Mechanisms of evasion of IR by EC bacteria & parasites
v.+ve feedback & cross regulation of Th subsets
vi. Cytokines that stimulate hematopoesis
vii. Regulatory proteins of complement components.
viii.Hapten

3-Give a short account on Clinical aspects of complement.

4-Enumerate biological activities of complement,give an account on 1 of them

5-Define heterophil Ag,mention its practical applications

6- Name mechanisms by which Abs eliminate Ag from the body

7-Give reason :

i.T helper cell is important in isotype switch of B cell
ii.C3b is an important complement component
iii.Inherited deficiency of complement may lead to angioneurotic edema
iv.Both interferon & IL 4 influence outcome of class switch.

Immunology 5

Hypersensitivity

Diseases associat th humoral immunity

Type I hypersensitivity Immediate or anaphylactic	Type II hypersensitivity Cytotoxic or cytolytic	Type III hypersensitivity Immune complex

Type I (Immediate or Anaphylactic) type

Mechanism

I-1st exposure to Ag ⟶ Sensitization

1-Entry of allergen

Any substance that triggers **allergic reactions** in the body

Types

- **Pollen** , certain foods
- **Drugs : penicillin**
- Serum proteins ← Albumin, Antitoxic From Animals (Against Diphtoria)
- Bee venom

2-Allergen is taken by APCs & digested

Fragments are presented to **Th2** (genetic predisposition is important) (Overactive Th2 & weak Th1)

3-Th2 secrete IL4,13 & 5 ⟶ ⊕ of B cells ⟶ IgE secretion

4-Sensitization

IgE enters the circulation

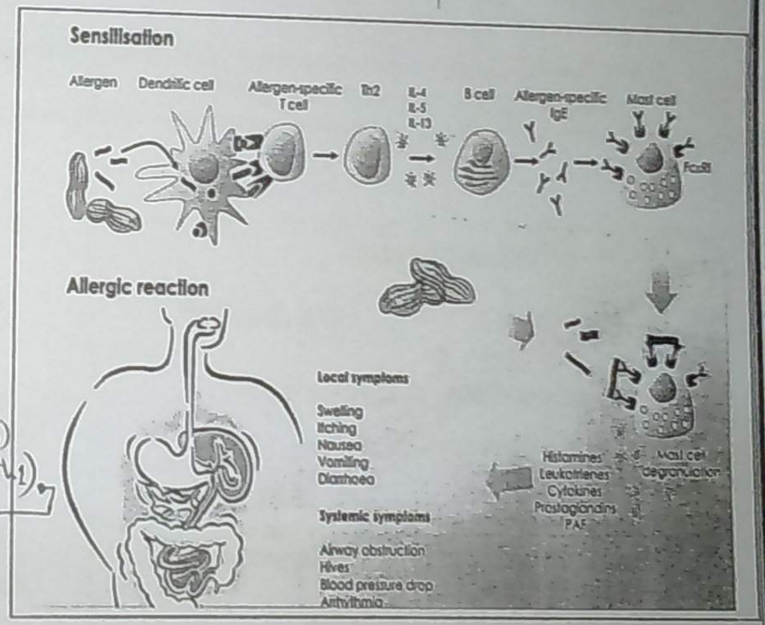
Attachs by its Fc to **Fcε R** on the surface of **mast cells & basophils**

Individual becomes *sensitized*

Requires 1w

Millions of IgE mol.are synthesized

Attach to **thousands of** mast cells & basophils



II - 2nd exposure to allergen ⟶ Degranulation

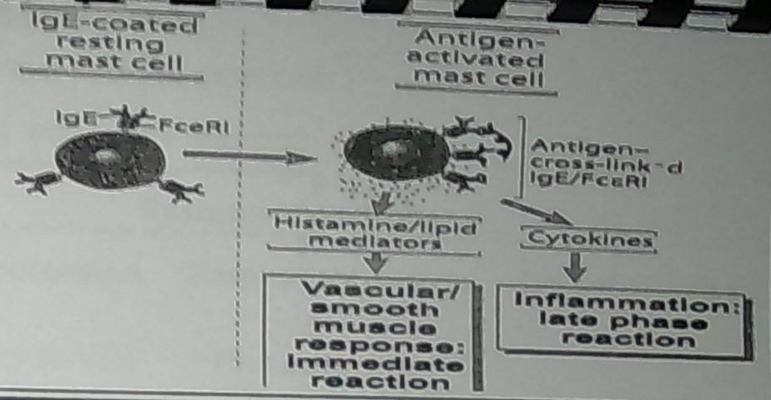
On subsequent exposure to the same allergen

⬇

Binds to **Fab of IgE Abs cross-linking** them

⬇

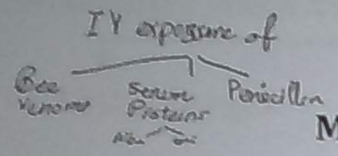
Degranulation of mast cells in tissues & basophils in blood



	III-Early phase reactions	IV-Late phase reactions
1-Onset after reexposure to Ag	Within **minutes**	Within **hours**
2-Mediators	***Physiological mediators*** **a.Histamine** & heparin ⟩→ 2 H b.PGs ,proteolytic enzymes & **PAF** c.Leukotrienes & **ECF-A**	***Cytokines*** **TNF α & IL 3** → Recruitment of neutrophils, eosinophils &Th2 **IL 4,13 & 5**
3-Effects	***a.VD &↑ capillary permeability*** ***b.Sm contraction & ↑ mucus secretion*** ***c.⊕ of nerve endings in skin*** Itching Pain	a. TNFα → ⊕ ***neutrophils*** IL5 → ⊕ ***eosinophils*** Release **proteases** → Tissue damage ***b. Th2 produces*** more IL4,13 &5 → Exacerbation

Clinical presentations

In respiratory passages , intestinal walls & skin (sites of mast cells)



I-Systemic anaphylaxis (fatal within few minutes)

Mechanism

Allergen enters blood for **2nd time**

↓

Cross links preformed IgE on mast cells&basophils

↓

Degranulation & **immediate release** of mediators

Systemic reactions

- **Edema & hypotension** (↑permeability & VD)
- **Respiratory distress** (Sm contraction)
- **Urticarial rash & itching**

II-Localized anaphylaxis : atopy (atopia = extraordinary)

RT, GIT, Skin

RT → **A- Airborne allergens** → **Allergic rhinitis & bronchial asthma**

	Allergic rhinitis	Bronchial asthma
1-Allergens	✓ i.Plant pollen ii.Animal hair & dander iii.House dust iv.Fungal spores v.Mites العث	
2-Mechanism	*Degranulation of mast cells in:*	
	MM of eye & upper RT	**Lower RT**
3-Symptoms	i.Red itchy tearing eyes ii.Congested nasal passages iii.Coughing & sneezing	*Difficulty in breathing & wheezy chest due to:* Sm contraction Bronchial narrowing by: i.VD &↑ permeability ii.↑ mucus Alveolar overdistension with fluids &mucus

GIT → **B-Food & Drug allergens** (ingestion)

Affect GIT → ***Local reactions***

Abdominal cramps,vomiting & diarrhea

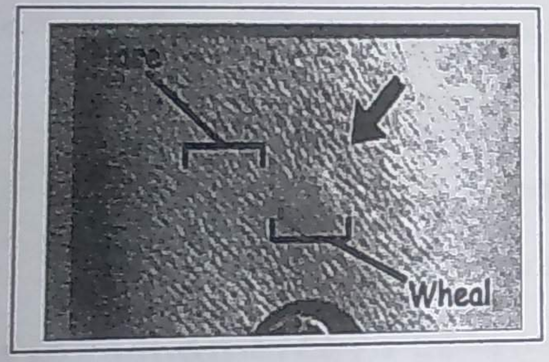
Absorbed in blood

- Reach **skin** → Urticarial rash
- Reach **lungs** → Asthmatic attacks

Diagnosis

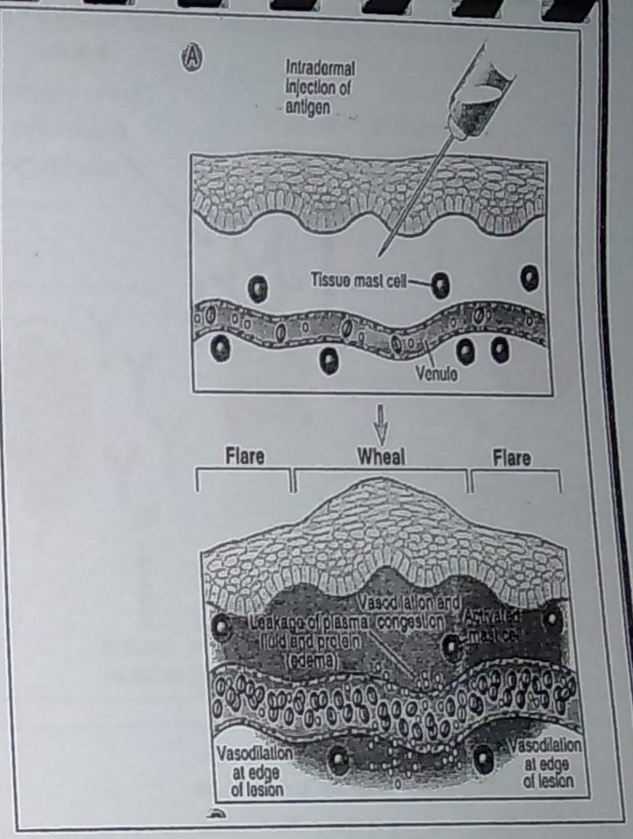
I-Allergy skin test ⟶ determine causative allergen

Test allergen	Method	+ve result
i. Pollens. ii.Grasses & molds iii.Cat dander iv.Food ***v.Penicillin*** (before inj.)	***Pricking*** the skin in forearm & back with a sterile lancet	*Wheel & flare reactions within **15-20 min*** (small circles of itchy inflammation like mosquito bite)



♣ Based on its size, sensitivity is assessed as:

- Mild
- Moderate
- Severe



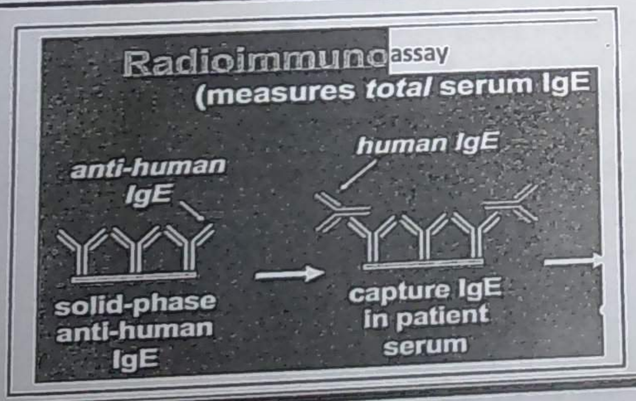
II-Allergy blood tests ⟶ measurement of serum IgE

Total IgE :

by RIA

(Radioimmunoassay)

↑ in *some* allergic pts

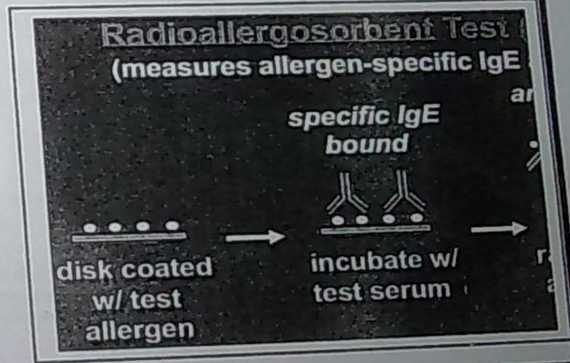


Specific IgE :

by RAST

(Radioallergosorbent Test)

Specific against *certain allergen*



Management

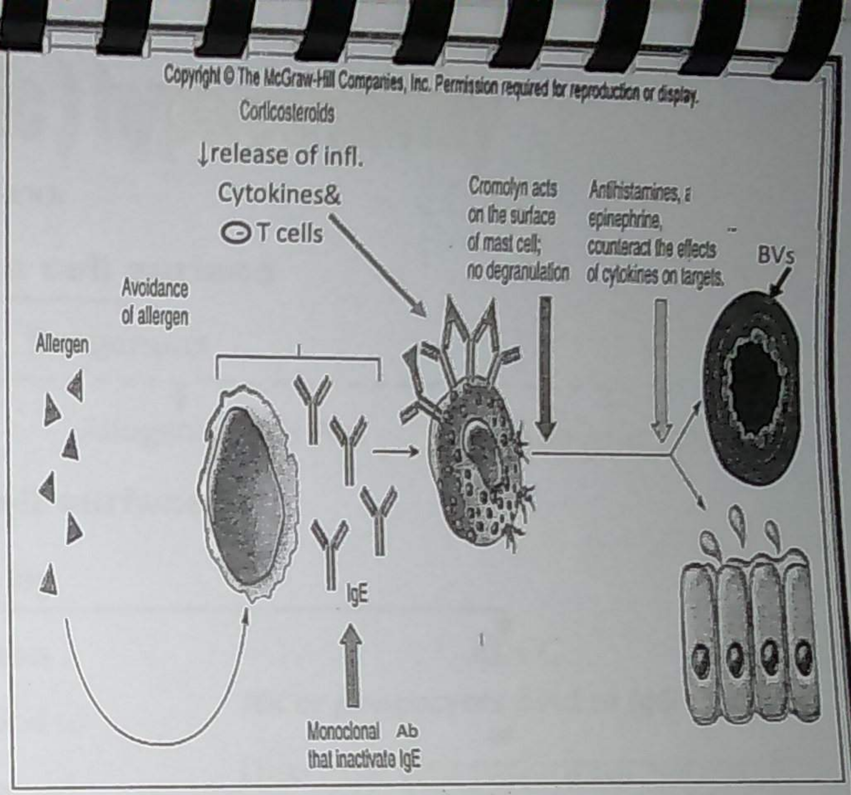
I-Identifying & avoiding allergen (if possible)

The *most effective* way of prevention

II-Drugs

Relieve symptoms or prevent release of chemical mediators

Epinephrine	Corticosteroids	Mast cell stabilizers	Anti
(life saving)	↓ inflammation	(Na chromoglycate)	histaminics
Relaxes Sm & constricts BVs	↓ all immune cells	⊖ mast cell degranulation	



IV-Monoclonal Abs : Anti IgE

Prevent IgE from binding to mast cell

IV-Allergen immunotherapy : desensitization

Indication

Failure of medications to control allergy symptoms

Method

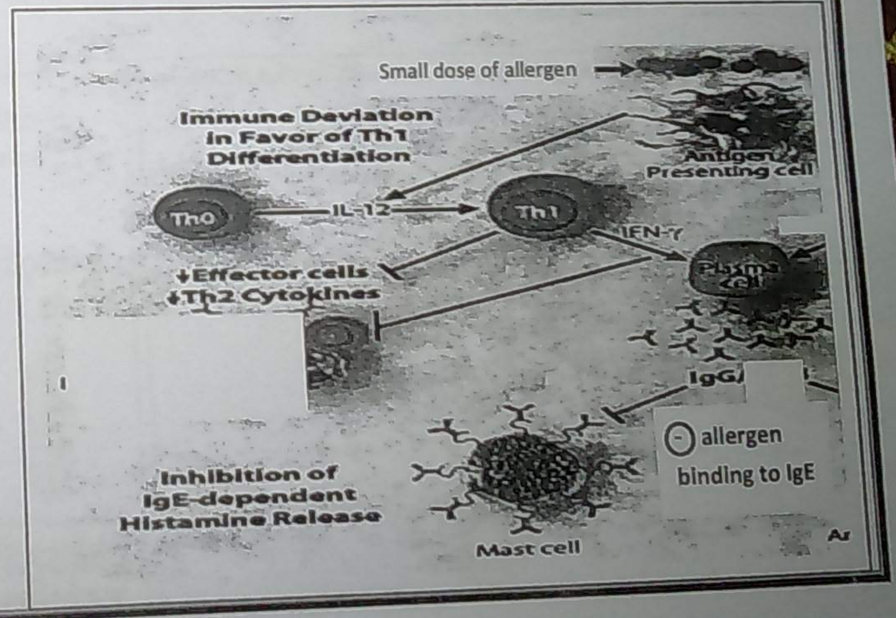
Gradually ↑ allergen doses are injected SC

⊕ *production of IgG* (Blocking Antibodies) rather than IgE

Capture & **neutralize Ag**

before reacting with IgE bound on mast cells

(prevent crosslinking)



Type II (Cytotoxic or cytolytic) hypersensitivity

Mechanism

1-IgG or IgM against Ag on cell surface

Endogenous

Due to failure of tolerance

Exogenous

Hapten (drug) or organism

Allogenic RBCs Ags

Allogenic graft cells

2-Ab binds to Ag on cell surface

3-Lysis of cell by

Complement activation (classical pathway)

MAC (C5b6789)

create pores in cell

Opsonization

Phagocytes bind to

IgG or ***C3b*** on cell

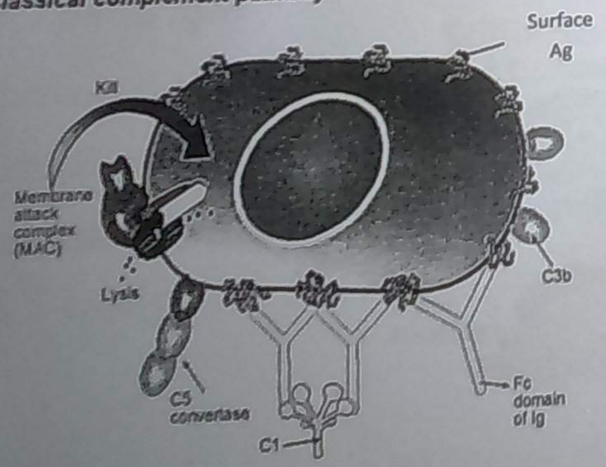
ADCC

NK or phagocytes bind to IgG on cell

Discharge their perforins,granzymes& proteolytic enzymes

Type 2 - antibody-dependent cytotoxicity

Figure 2a: Classical complement pathway



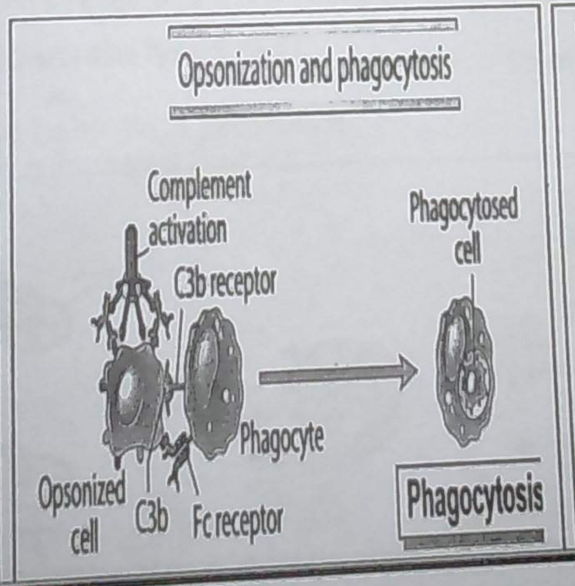
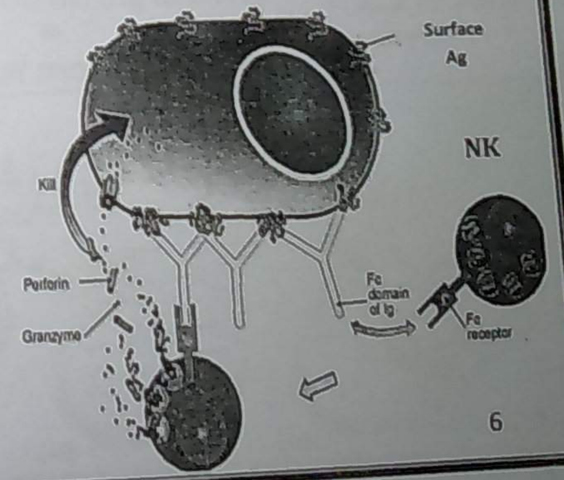


Figure 2b: Antibody dependent cell cytotoxicity (ADCC)



Clinical syndromes

Immune destruction of blood elements			Other syndromes	
Allohemolysis	Autohemolysis	Autolysis of Granulocytes &Platelets	Exogenous Ags	Endogenous Ags

I – Allohemolysis

ABO compatibility

(commonest cause of transfusion reactions)

ABO Ags are allogenic

(differ between persons)

⬇

If **A+ve** person

is transfused with

B+ve RBCs

⬇

Natural antiB IgM

rapidly hemolyse RBCs

in circulation

by complement

(rapid IV hemolysis)

Rh incompatibility (Rh factor or D Ag)

Mechanism

Fetal Rh+veRBCs leak into Rh-ve mother

circulation during birth of **1st child**

⬇

Sensitizes mother to produce **IgG**

⬇

Cross placenta in subsequent pregnancies

⬇

Destroy fetal RBCs

(Erythroblasts released from fetus to compensate lysed cells)

⬇

Stillbirth or baby with **jaundice**

↳ (Immune erthroplastosis Fetalis).

Prevention

AntiD injections

Given to mother

within 72 hrs

of **1st delivery**

of RH+ve baby

⬇

Destroy any

leaking fetal RBCs

to mother blood during delivery

⬇

No ⊕ of mother IS

Treatment

Exchange

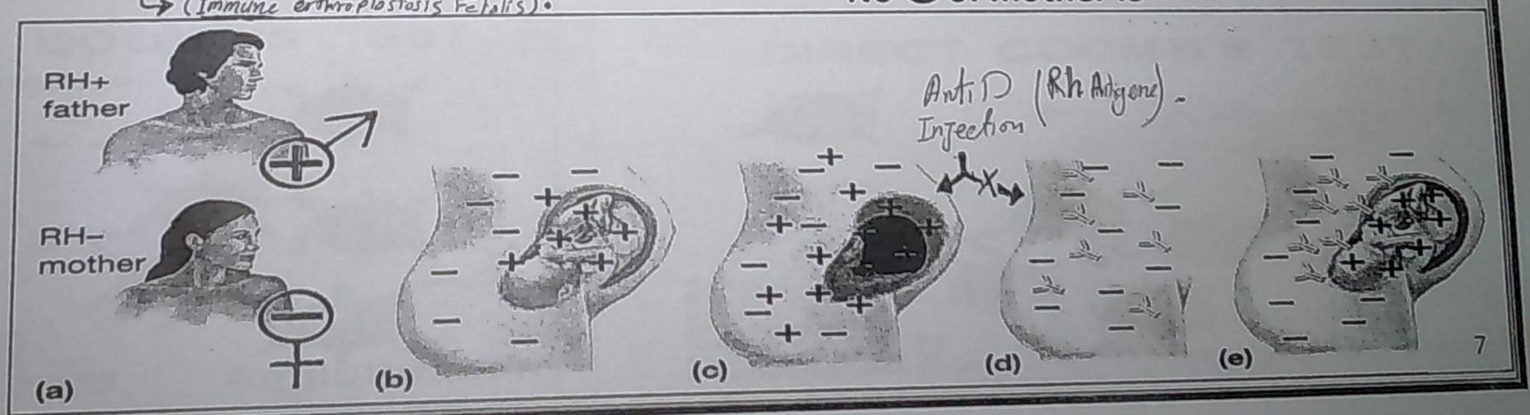
transfusion

of fetal RBCs

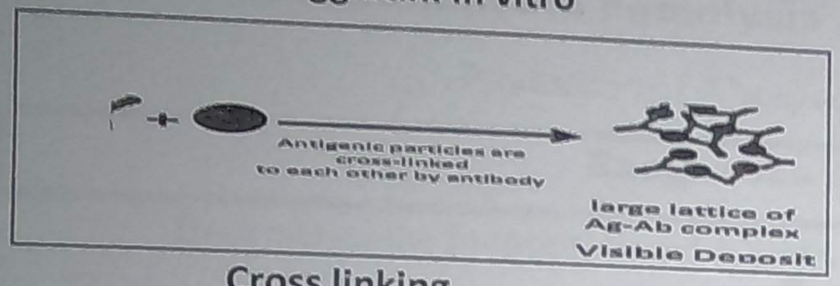
with **RH-ve**

cells

to avoid its distruction by maternal Antibodies

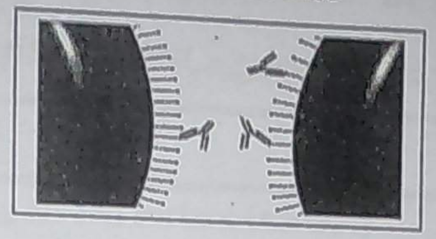


Normal agglutin. in vitro



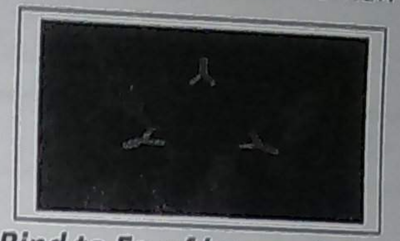
Cross linking

Incomplete Rh Abs



No cross linking

Coombs'reagent (Antihuman Igs)



Bind to Fc of human IgG

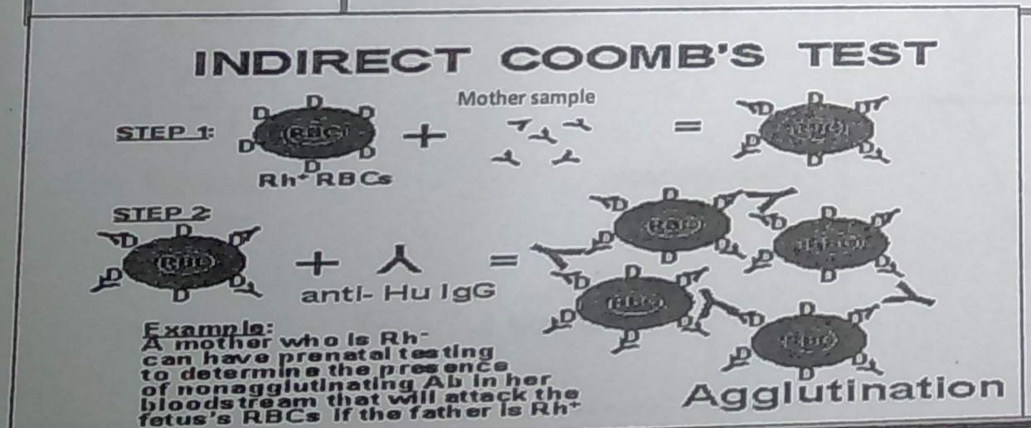
Diagnosis : Coombs' test

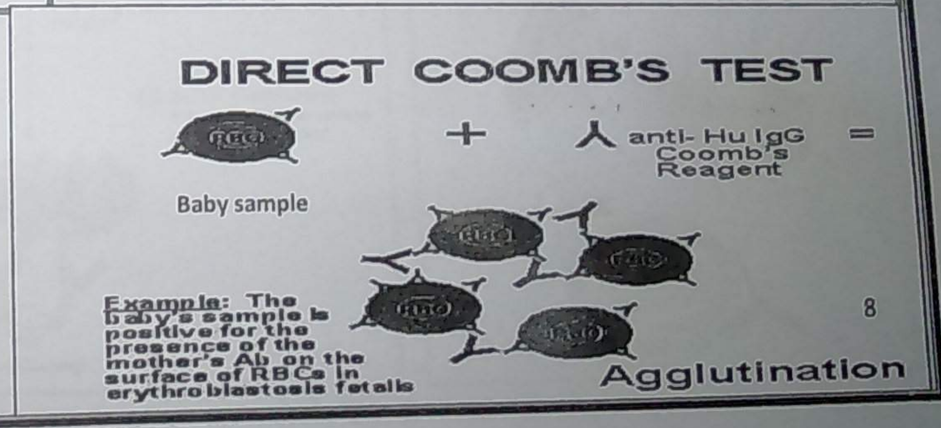
Aim : Detect **incomplete Rh Abs** (IgG):

They coat Rh+ve RBCs , but ***can't bridge*** between them to cause agglutination

Cause agglutination only after **addition of Coombs'reagent** (antihuman globulin)

	Indirect coombs'test	**Direct coombs'test**
1-Uses	Detect **free Rh Abs** in serum of **mother**	Detect ***Rh Abs coating RBCs*** in serum of ***newborn***
2-Method	i.Blood sample from mother **ii.Add Rh+ve RBCs** + Coombs'reagent	i.Blood sample from newborn ii.Add Coombs'reagent
3-+ve result	**RhAbs coat Rh+ve RBCs** ↓ Agglutination by Coombs'reagent	***RBCs coated with RhAbs*** ↓ Agglutination by coombs"reagent





II-Autoimmune hemolysis , thrombocytopenia or granulocytopenia

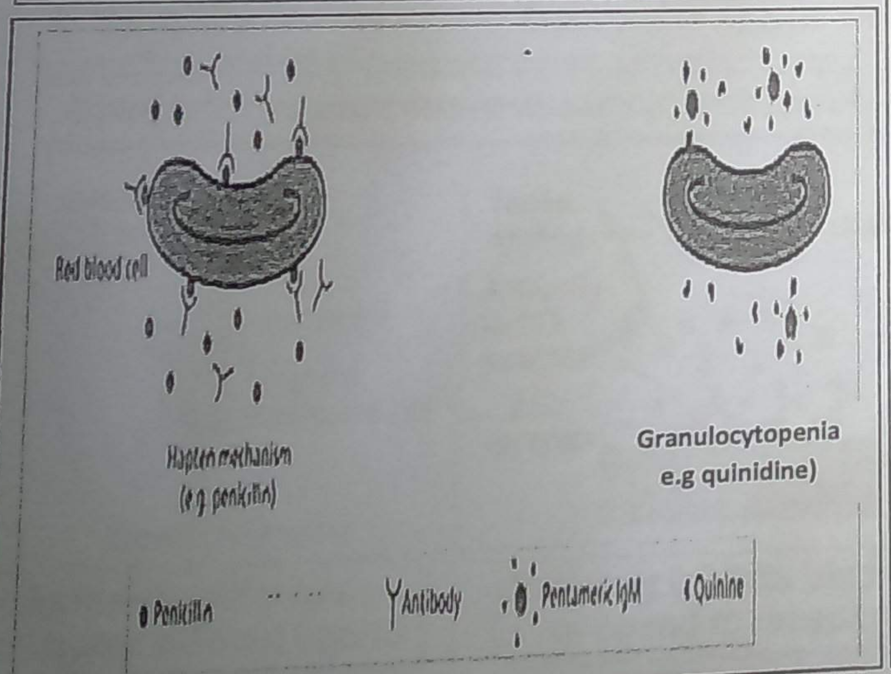
Production of Abs against ***pt own*** RBCs,granulocytes or platelets

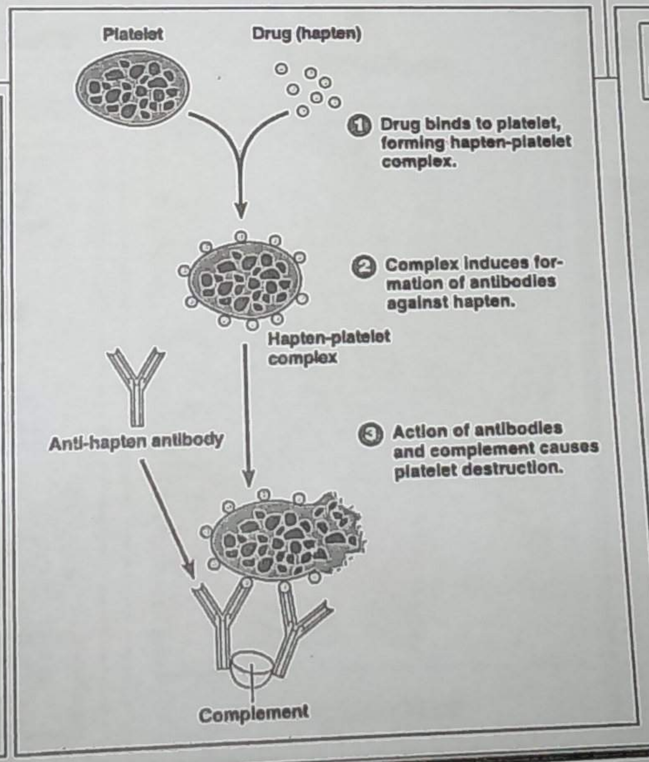
Exogenous Ags	Endogenous Ags
Drug metabolite **(hapten)** bound to protein Ag on cell surface **(carrier)**	**Autoimmune ds**

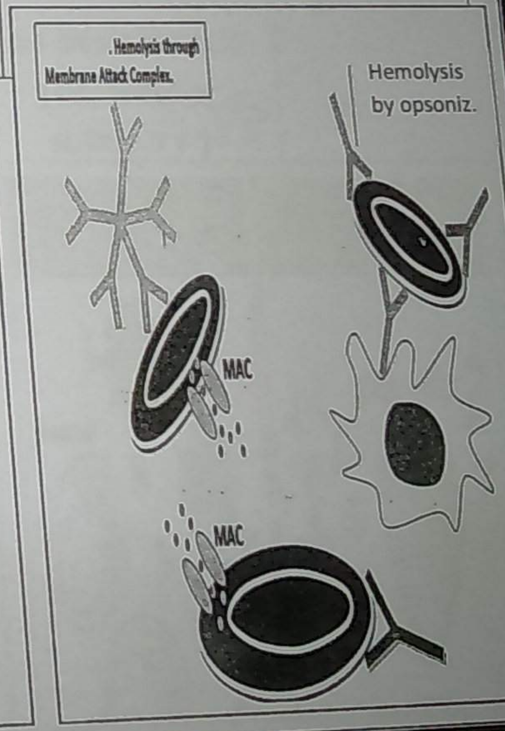
RBC لـ بتمسك فـ الـ

Abs are cytotoxic to cell-drug complex

Hemolytic anemia	**Granulocytopenia**	**Thrombocytopenic purpura**
♦ **Penicillin**	Quinidine	Acetaminophen استيك منه فيه رجلك نزيف
♦ Chlorpromazine	(antiarrythmic)	(analgesic)
(antipsychotic)		







III - Other clinical syndromes

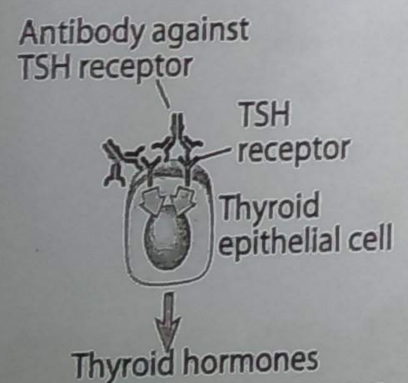
Endogenous

Antireceptors (type V hypersensitivity)

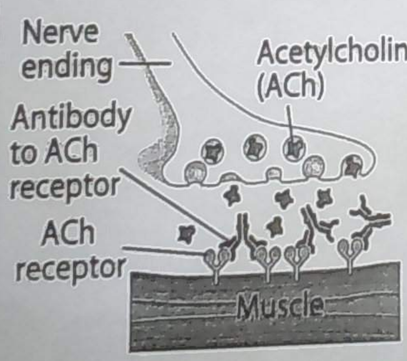
Non-cytotoxic AB ← Abs ***block ability of receptor*** to bind with its ***natural ligand*** without ⊕ complement

⊕ of receptor signaling	⊖ of receptor signaling
Grave's ds	***Myasthenia Gravis***
IgG binds& ⊕ TSH receptors on thyroid cells	IgG binds & ⊖ acetylcholine receptors
↓ Hyperthyroidism (Grave's diseases)	↓ Progressive muscle weakness

Abnormal physiologic responses without cell/tissue injury



Antibody stimulates receptor without ligand



Antibody inhibits binding of ligand to receptor

Good pasture's syndrome

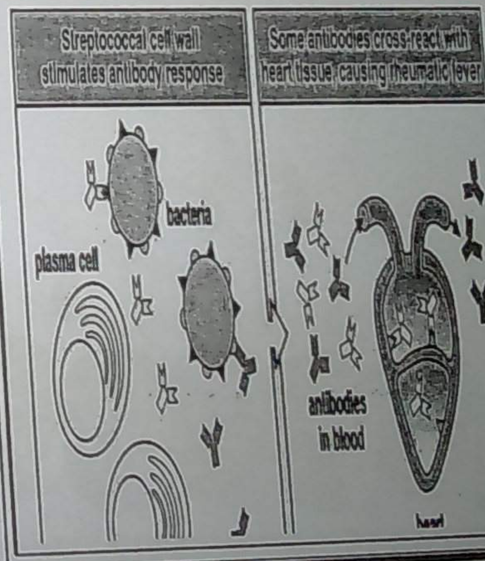
IgG binds glycoproteins **on lung & glomerular cells** ↓ Destruction

Goodpasture syndrome

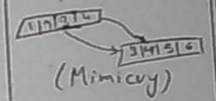
Exogenous

Rheumatic fever

Antistreptoccal IgG cross react with **heterophil Ag** on **heart** muscle **(molecular mimicry)**



Hyperacute graft rejection



Type III (Immune complex) Hypersensitivity

Etiology & Mechanism

1-Ag excess

- **Exogenous**
  - Chronic infection (bacterial,viral& parasitic)
  - Non microbial Ags (Insulin)
- **Endogenous**
  - Self Ag in autoimmune ds

2-Production of **large amounts of Abs : IgG** (mostly) & IgM

3-Formation of **large amount of of ICs** (Immune complex) (Ag+Ab)

4-Failure of IS to eliminate them

5-Excess ICs pass between endothelial cells of BVs especially in skin , joints & kidney

Type 3 - immune complex hypersensitivity

Figure 3a

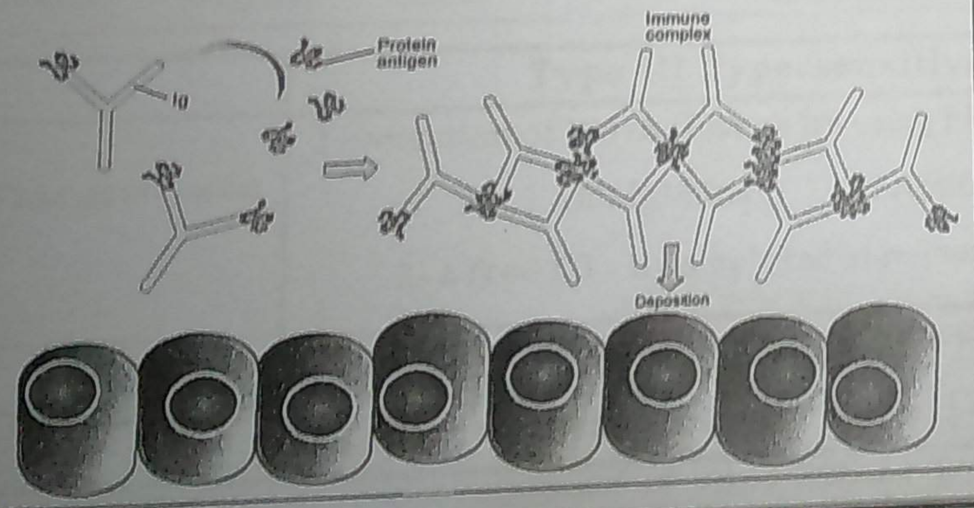
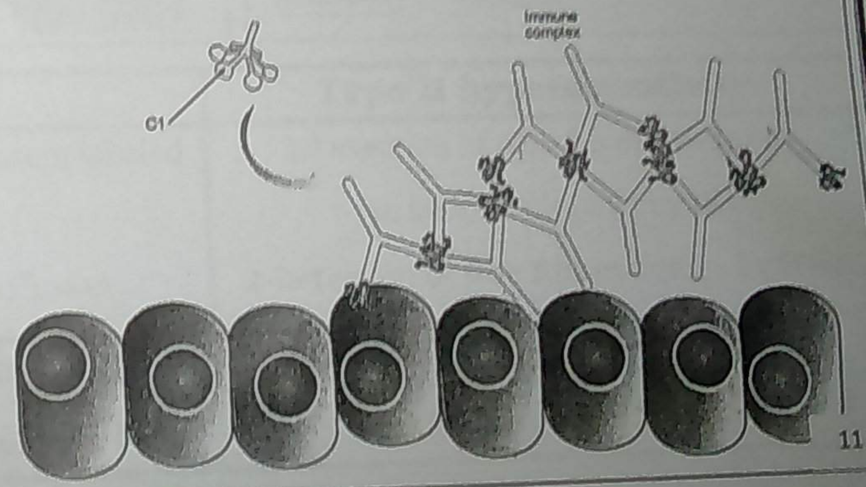


Figure 3b

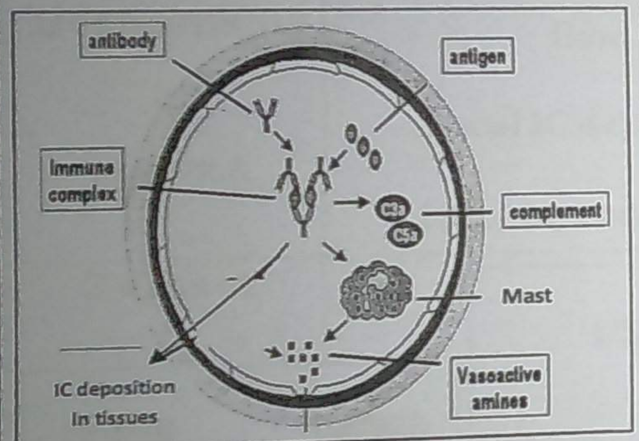


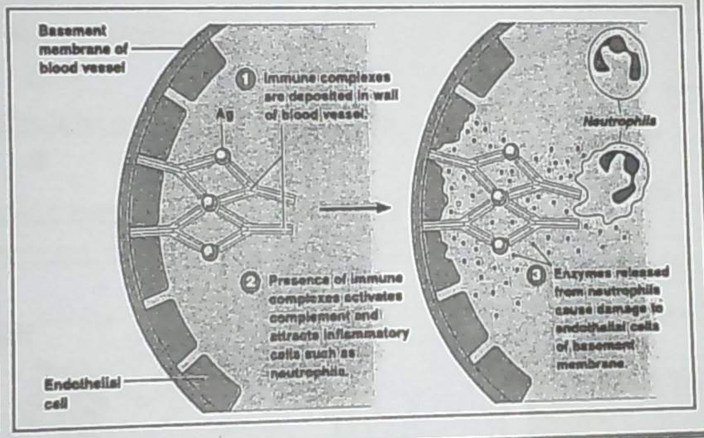
6 -Tissue damage

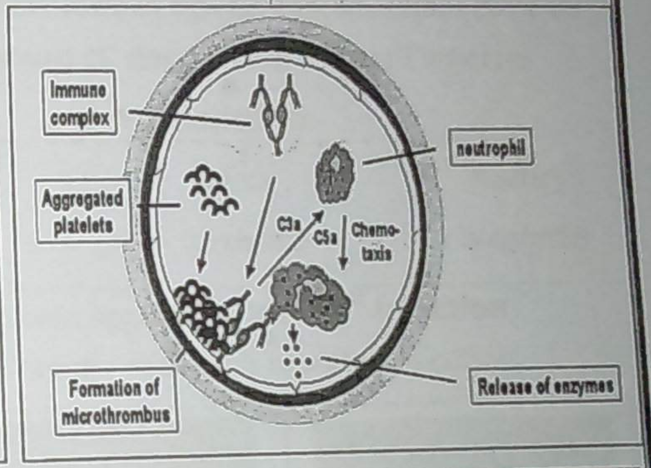
ICs activate excess complement by classical pathway

Platelet aggregation

C5a & C3a (anaphylatoxins)	C5a (chemotaxis)	MAC (C5b6789) (Membrane Attack complex)	(By ICs & inflam.mediators)
Release mast cell mediators	Attract neutrophils	Attaches to cell surface	**Microthrombus**
↓	↓	↓	↓
↑ vascular permeability	Release of lysosomal enzymes	***Lysis of tissue cells***	***Local ischemia***
↓	↓		
IC deposition in tissues	***Vasculitis & lysis of tissue cells***		



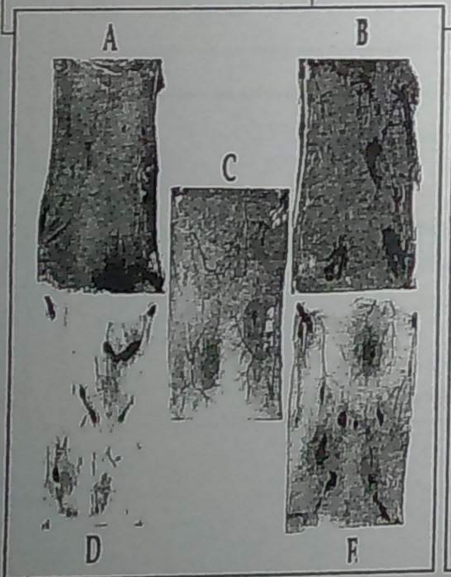


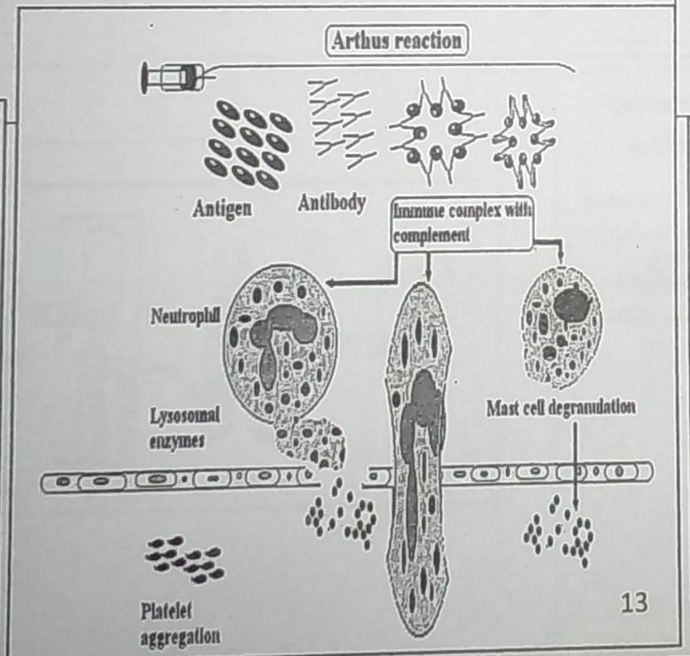


	Type III hypersensitivity	Type II hypersensitivity
Diagnosis	1-Detection of **ICs in tissues by** using Fluorescin labeled i.Anti IgM&IgG ii.AntiC3b 2- ↓ **free C3** : By single radial immunodiffusion	1-Detection of **Abs & complement** in lesions biopsy : by IF 2-Detection of **free Abs** in tissue : by ELISA
Treatment	1-Corticosteroids : ↓ inflammation **2-Plasmapheresis** (in severe cases): ↓ circulating ICs ↳ Replacement of Plasma containing IC by Fresh Frozen plasma.	1-Anti-inflammatory drugs 2-Immunosuppressive drugs

Clinical presentations

	① Arthus reaction (localized)	② Serum sickness (systemic) (More Common than Type I)
1-Etiology	Repeated **SC injection of:** ***i.Insulin*** ***ii.Penicillin*** ***iii.Rabies vaccines*** (الصراع الكلبي)	Injection of **foreign serum:** (IV) **i.Animal serum** (containing antitoxins) **ii.Plasma transfusion** (Albumine)
2-Mechanisms & lesions	**ID** Ags can't diffuse out rapidly ⬇ Bind to circulating Abs ⬇ **Local IC deposition** in small arteries ⬇ *Local cutaneous* ***vasculitis & necrosis***	**Excess Abs** are formed against foreign serum proteins ⬇ **Widespread IC deposition** in small arteries ⬇ **Vasculitis in** Skin → ***Rash*** ; Joints → ***arthritis*** ; Kidneys → ***Nephritis***
3-Onset		Symptoms appear **1w after 1st injection** ⬇ More rapidly with each repeated injection





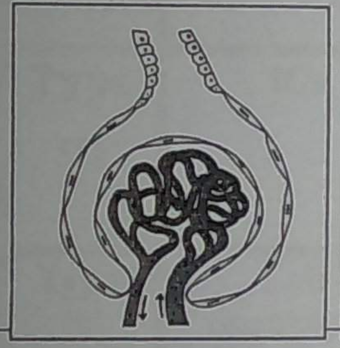
III-Other clinical syndromes

Exogenous Ags

Chronic microbial ds

complicated by IC formation

Bacterial — ***Post-streptococcal glomerulonephritis***



Viral — ***Hepatitis viruses*** (B, C)

Farmer's lung

(Ext.allergic alveolitis)

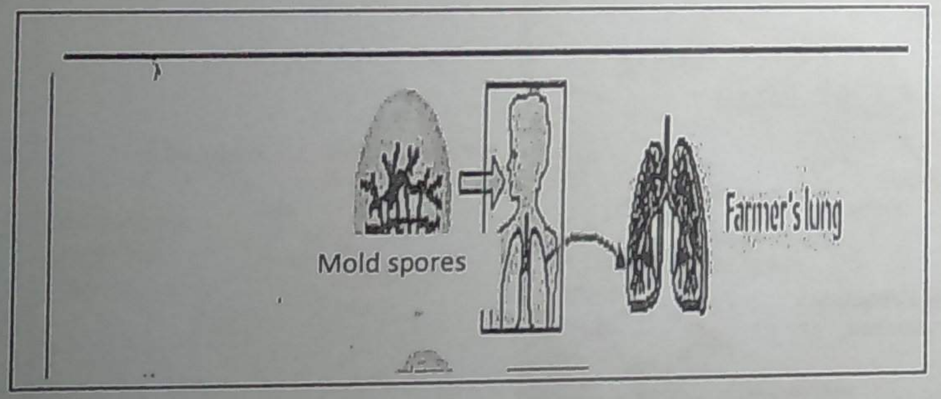
IgG against

→ mold **spores** &

→ **pigeon** feces

⬇

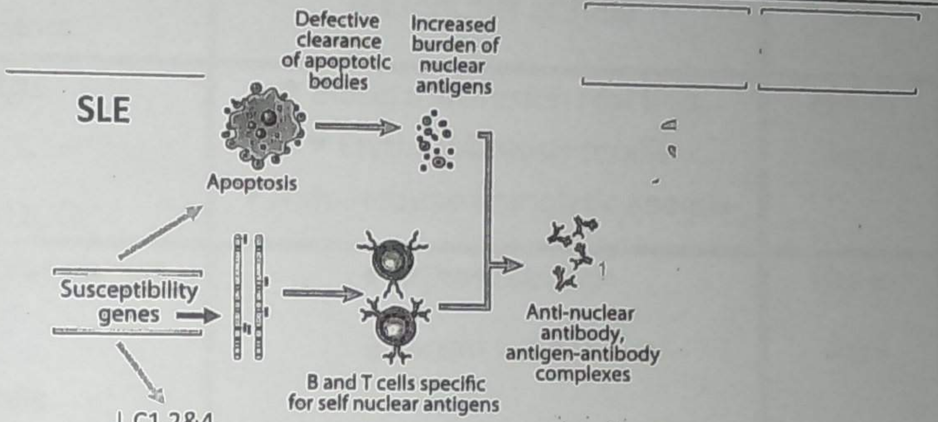
IC deposition in lungs

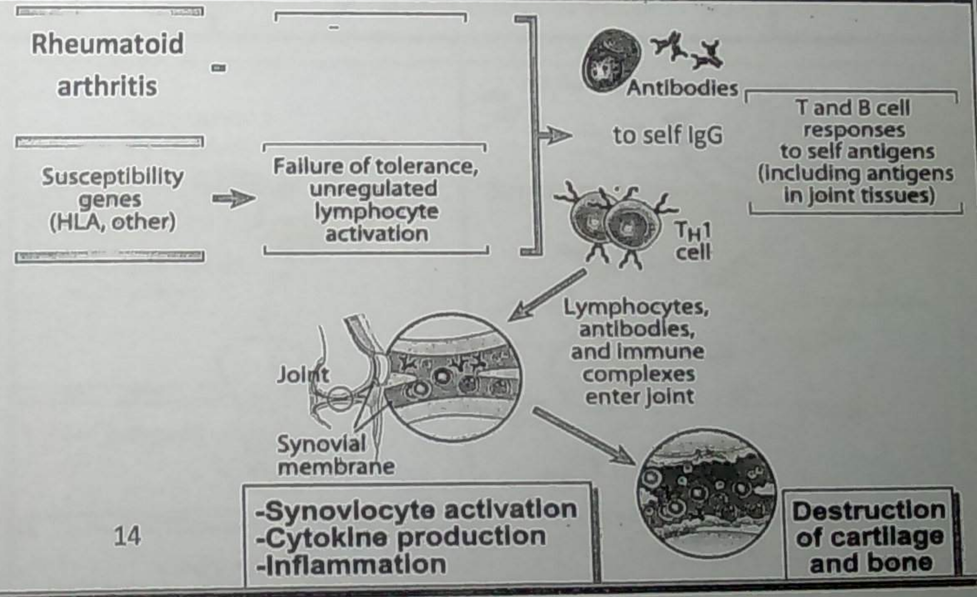


Endogenous Ags

Auto Abs against self Ags

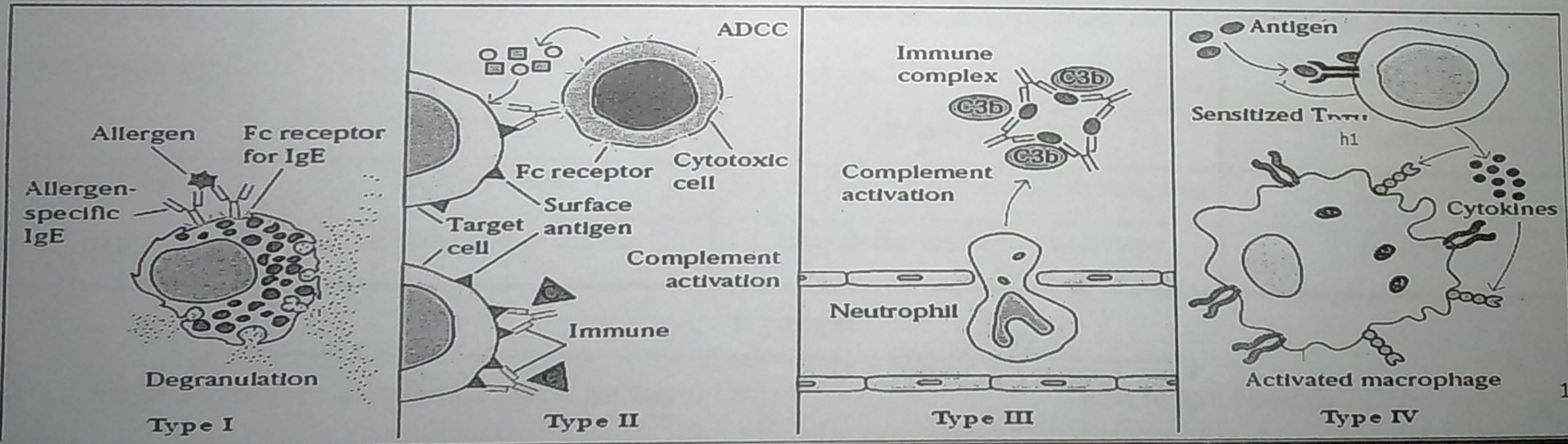
♦SLE **♦Rheumatoid arthritis**





Comparison between different types of hypersensitivity

	Main factor	Pathogenesis	Examples	Time
Type I	IgE	Ag induces cross linking of ***IgE bound to mast cells &basophils*** ↓ Release of vasoactive mediators	♣ Systemic anaphylaxis ♣ Bronchial asthma	Min to hrs
Type II	IgG& IgM	Ab against ***cell surface Ags*** ↓ Cell destruction by: ↓ Complement activation & ADCC	♥ Blood transfusion reaction ♥ Erythroblastosis fetalis ♥ Autoimmune hemolytic anemia	Hrs to days
Type III	ICs	Ag-Ab complexes ***deposit in different tissues*** ↓ ⊕ complement ↓ ↑↑ infiltration of **neutrophils**	♠ Arthus reaction ♠ Serum sickness	Hrs to days
Type IV	Cell mediated	***Sensitized Th1 release cytokines*** ↓ ⊕ MQ or Tc	♦ Contact dermatitis ♦ Tuberculous lesions	2-4 days



Autoimmune diseases

Mechanisms of tissue damage in autoimmune diseases

Ab mediated (type II&III) : By Ig G (usually) & IgM ⊕ of complement &opsonization of injured cell promote inflam. ⬇ More damage to self Ags

Cell mediated (type IV) CTL react against self Ag

Overlap between Ab&Tcell Damage is mediated by both

	Disease	Target Ag	Clinical finding
A- Type II hypersensitivity	1-AI hemolytic anemia	***RBC*** membrane protein	Anemia
	2- Rheumatic fever	***Myocardial*** Ag	Myocarditis
	3-Good pasture's syndrome	Protein in BM of ***glomeruli & alveoli***	Nephritis&lung hge
	4-Myasthenia gravis	***Acetyl choline receptors*** on muscle	Muscle weakness
	5-Grave's disease	***TSH receptor*** on thyroid	Hyperthyroidism
B-Type III hypersensitivity	*1-SLE*	**DNA** & nucleoproteins	Nephritis,vasculitis,arthritis.
	2-Rheumatoid arthritis	**Ab** (anti Ig Ab are produced in joints)	Arthritis
	3-Poststrept.glomerulonephritis	**Glomerular** BM	Nephritis
C-Type IV hypersensitivity	1-Type I DM	Ags on ***Langerhans cells*** of pancreas	Diabetes
	2-Rheumatoid arthritis	Ag on the wall of ***synovium***	Arthritis

Types

Organ specific : Myasthenia gravis & Grave's ds

Non organ specific : SLE

Laboratory diagnosis

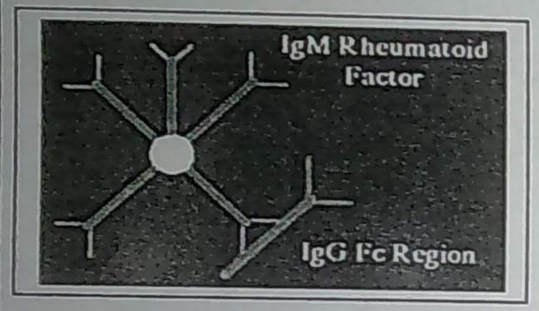
↑ serum Igs

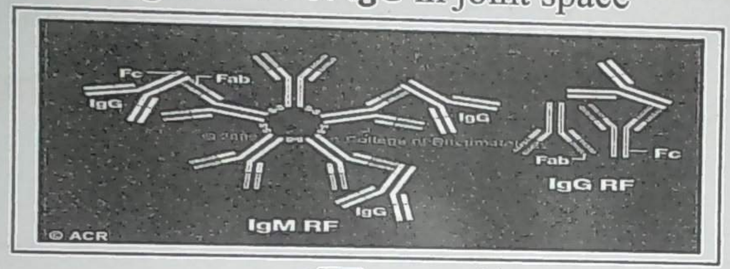
↓ complement levels

Detection of specific autoAbs in serum

Rheumatoid factor in rheumatoid arthritis

Abs against Fc of IgG in joint space





Antinuclear Abs in SLE

Detection of ICs in serum & tissues

By IF

Treatment

I-RAP

Replacement & symptomatic therapy

- ***Anti-thyroid drugs*** in Grave's ds
- ***Insulin*** in type I DM
- ***NSAIDs*** in rheumatoid arth.

Antagonists of proinflam.cytokines

Monoclonal Abs:Anti-TNFα in rheumatoid arthritis

Plasmapheresis

Remove offending ICs or Abs

II-Immunosuppressive drugs

⊖ cytokines secretion

- ***⊖ MQ cytokines*** Corticosteroids
- ***⊖ T cell cytokine:IL2*** Cyclosporine

⊖ T cell activation by ⊖ costimulation

Soluble CTLA-4

↓

Bind B7 mol.

↓

⊖ its binding to CD28

Block T cell proliferation

Methotrexate

Complement system

General characters

Synthesis

- ♥ Liver (mainly)
- ♥ MQ

Circulation

- ♣ Serum &TFs (except CSF&urine)
- ♣ *In inactive form (C1-C9)*

Activation

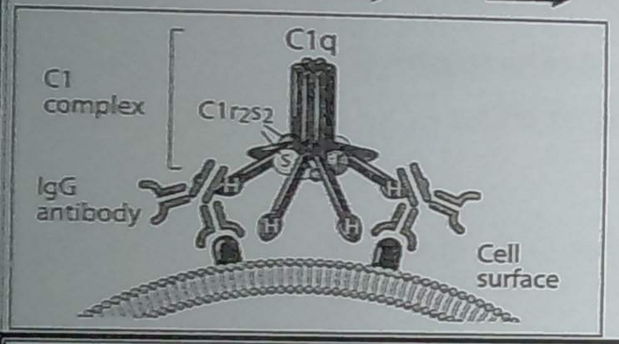
- **In cascade** manner ⊕ of C2 to C5 by enzymatic cleavage
  - a subunit: released
  - **b subunit: remains**

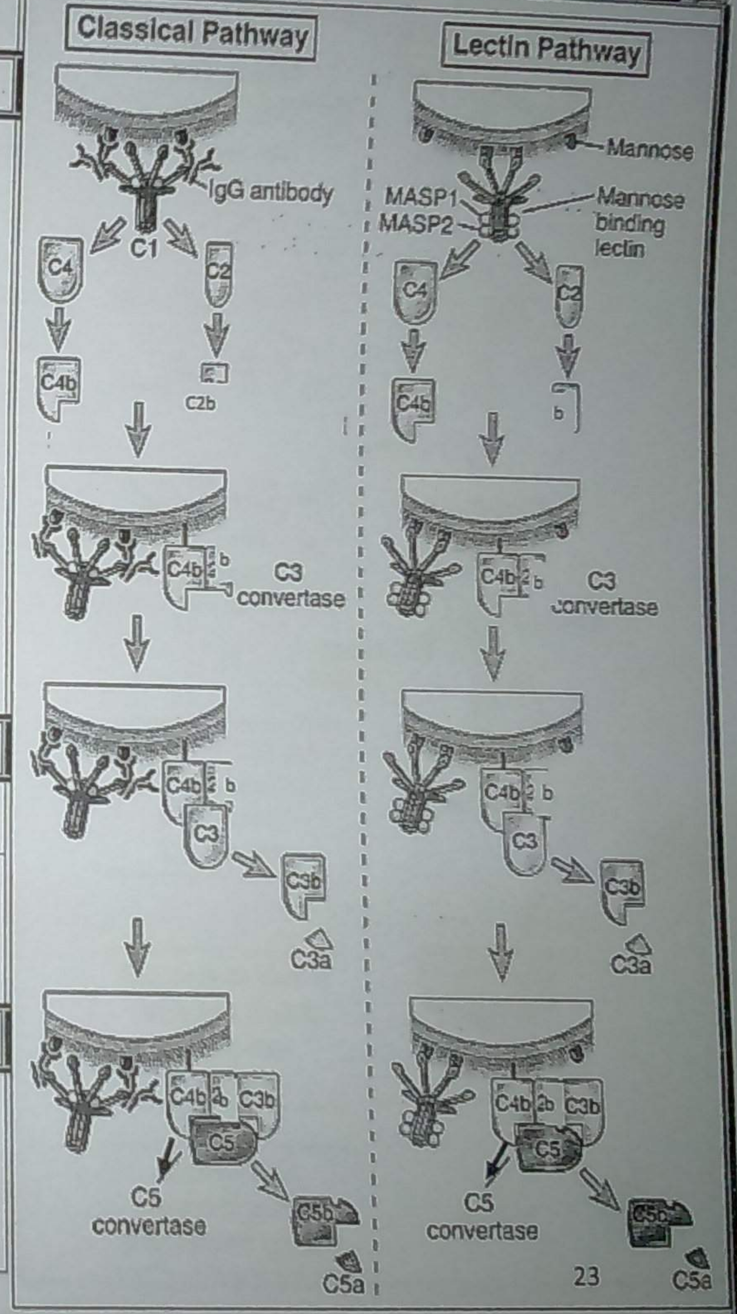
Importance

- **Elimination** of pathogen
- **Removal** of circulating & deposited **immune complexes**

Comparison between the 3 pathways of complement activation

	Classical pathway	**Lectin pathway**	**Alternative pathway**
1-Acivated by	**Ag-Ab** complex (***Adaptive*** immunity)	**Mannose** on pathogen surface (***Innate*** immunity)	**Pathogen** surface (***Innate*** immunity)
2-1st complement ⊕	C1	Mannose binding lectin (MBL)	C3b
3-C2 & C4	Activated		Not activated
4-C3 convertase	Same : ***C4b2b***		**C3bBb**
5- C5 convertase	Same : ***C4b2b3b***		***C3bBb3b***
6-Membrane attack complex (MAC)	***C5b6789*** (common final pathway)		

Classical pathway	Lectin pathway
1-Initiation & 1st complement activated	
Ab :IgM (most efficient) or IgG3,1,2 ↓ Binds Microbial surface or other Ags ↓ Conformational change of **Fc (CH2)** of Ab → ⊕ *of C1q* ⊕ → *C1r* ⊕ → *C1s* 	*Mannose binding lectin (MBL)* [structurally similar to C1q] ↓ Binds **Polysaccharide on microb.surface** (not found on human cells) ↓ Conformational change of **MBL** ↓ ⊕ *of MASP1 & MASP2* (man.bind.lect.assoc.protease) [structurally similar to C1r & C1s]
2-Formation of C3 convertase	
Activated C1 **cleaves C4 & C2** into:	Activated MASP1&2 **cleaves C4 & C2** into:
i. 2 **small** fragments **C4a & C2a : *Released*** into surrounding space	
ii.2 **large** fragments:**C4b&2b → *bind*** to bacterial CW → ***C4b2b (C3 convertase)***	
3-Formation of C5 convertase	
C4b2b bind & cleave **C3** into:	
i.**C3a** : ***released*** into surrounding space	
ii.**C3b : *Reacts*** with C4b2b ⟶ ***C4b2b3b (C5 convertase)***	



Alternative pathway

1-Initiation & 1st complement activated

Spontaneous cleavage of C3 in plasma at low rate

↓

C3b (quickly hydrolysed if no microbe in circulation)

↓

Binds **Microbial surface**

↓

Conformational change of **C3b**

2-Formation of C3 convertase

C3b binds to Factor B

↓

C3bB

↓

Factor D cleaves factor B in the complex

Ba	**Bb**
(small & inactive → ***released***)	(large & remains ***attached***)

↓

C3bBb (C3 convertase)

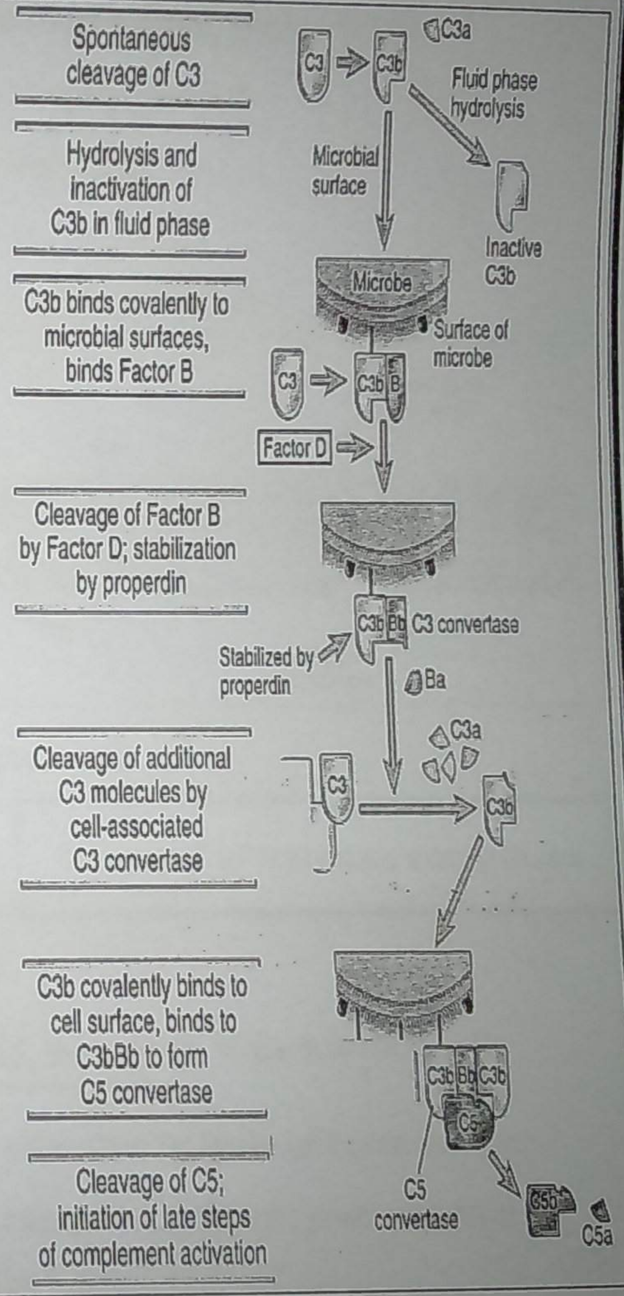
↓

Stabilized by **properdin** (Prolongs its action)

3-Formation of C5 convertase

*C3bBb bind & cleave **additional C3***

C3a	**C3b**
Released into surrounding space	***Reacts*** with C3bBb ↓ ***C3bBb3b (C5 convertase***.



4-Formation of MAC (Membrane attack complex.) **(common final pathway)**

C5 convertase bind &cleave **C5** into **C5a** (released into surrounding space) & **C5b**

↓

C5b binds **C6,7,8 & multiple mol.of C9** (C9 polymerized)

↓

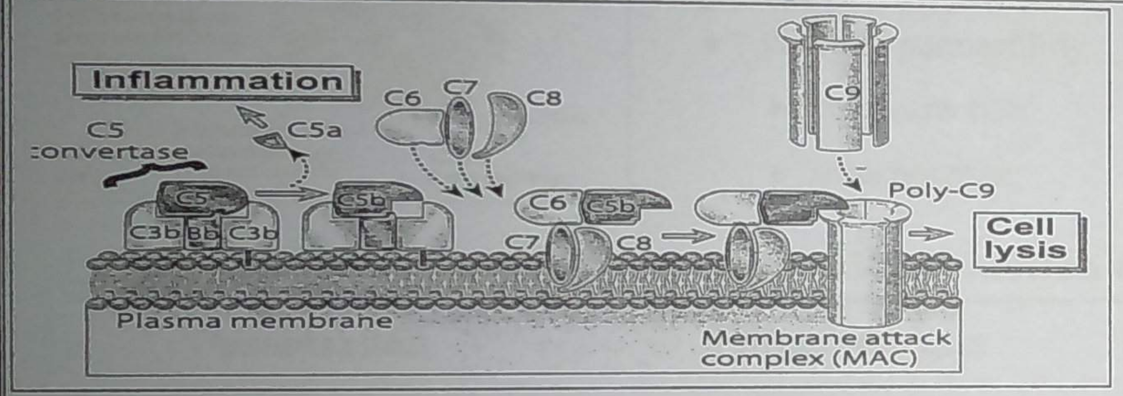
C5b6789 : Membrane attack complex (MAC)

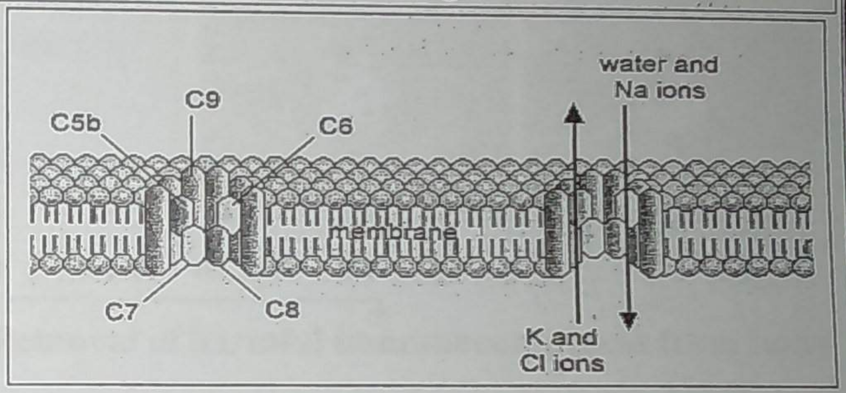
↓

Pores in target membrane

↓

↑ IC Na → entry of water → osmotic swelling → **Lysis of target**





Biological effects of complement

Cytolysis	Stimul. of inflam.response	Opsonization	↑ Ab production	Removal of immune complexes

1- Cytolysis : by *C5b6789 (MAC)*

Insertion of MAC into CM → lysis of many cells : **bacteria, viruses, fungi, parasites, VICs &tumor cells**

MAC is **more critical in lysis** of bacteria with **thin CW** (more vulnerable) e.g ***Neisseria*** ← due to deficiency in C5-8 Leads to recurrent Infection

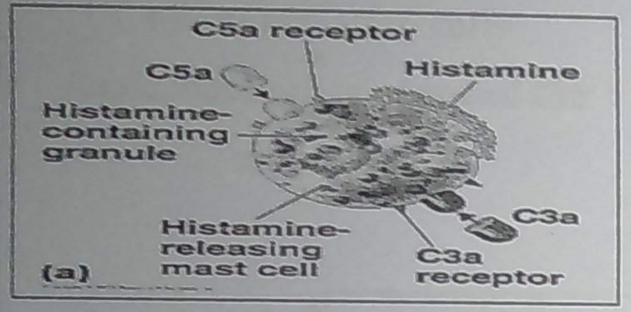
MAC is **less effective in lysis** of bacteria with **thick CW& capsule**.e.g ***Strept.pneumoniae***

II-Stimulation of inflammatory response

Chemotaxis : by C5a

Attracts phagocytes

to site of infection



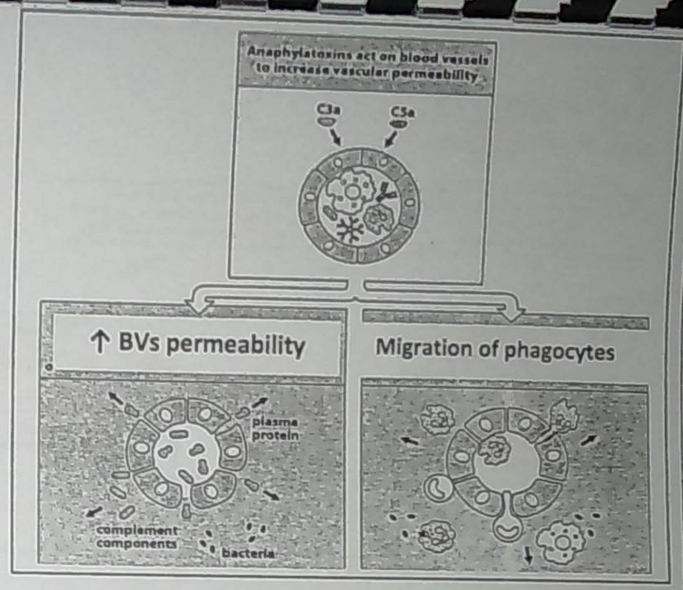
Anaphylaxis : by anaphylatoxins (C3a,4a&5a)

Attach to their receptors on mast cells

Degranulation & histamine release

Symptoms of anaphylaxis:

- ↑ vascular permeability
- Sm contraction
- Bronchospasm



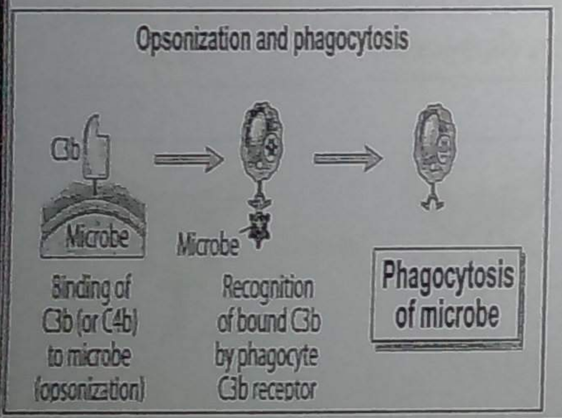
III- Opsonization,↑ Ab production & removal of ICs : by C3b

Opsonization

C3b coats **bacteria & viruses**

Binds to *C3bR* ***on phagocytes***

Facilitates phagocytosis

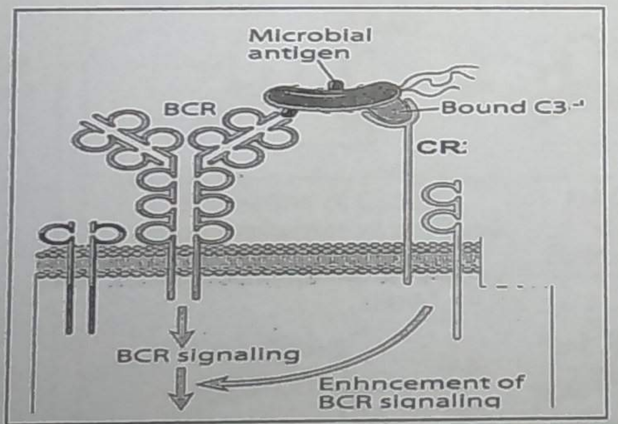


↑ Ab production

C3b binds to

C3bR on ***activated B cells***

↑ Ab production



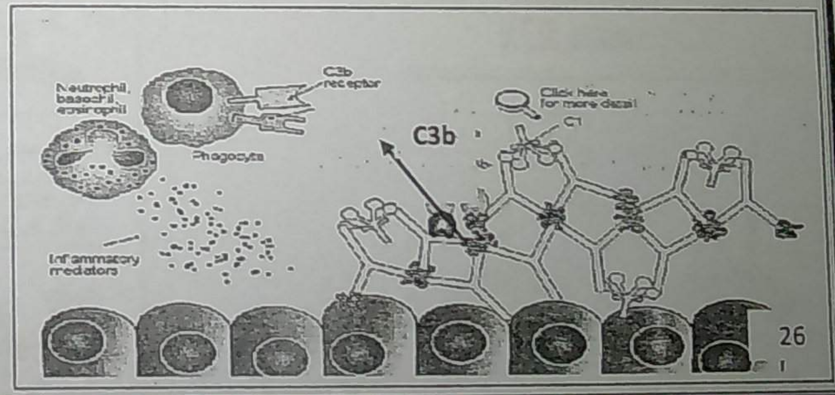
Removal of harmful immunecomplexes from body

C3b **deposits on ICs** surface

Facilitate their *clearance from circulation* ***by phagocyte***

Prevent their deposition in BVs wall

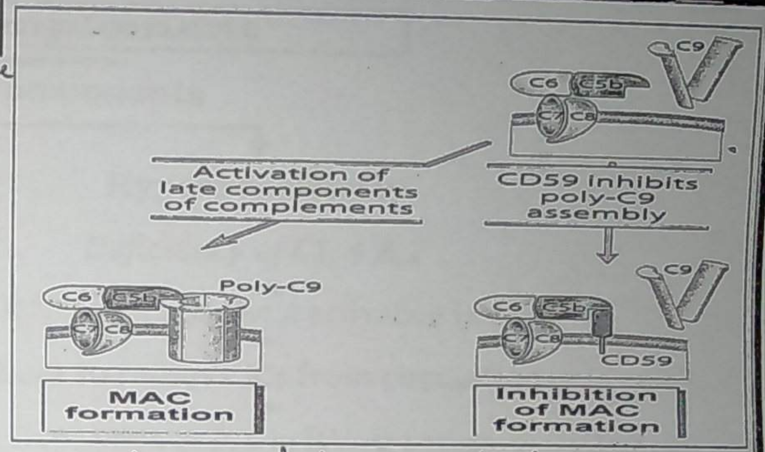
Prevention of tissue damage (Type III hypersen.)



Regulation of complement activation

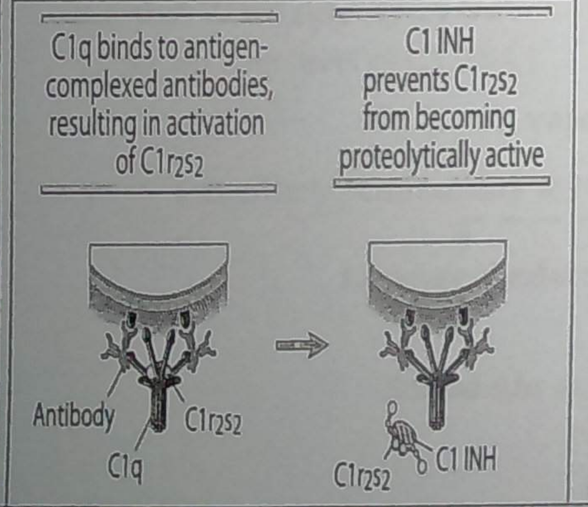
I-Proteins on surface of self cells → to avoid autoimmune diseases -

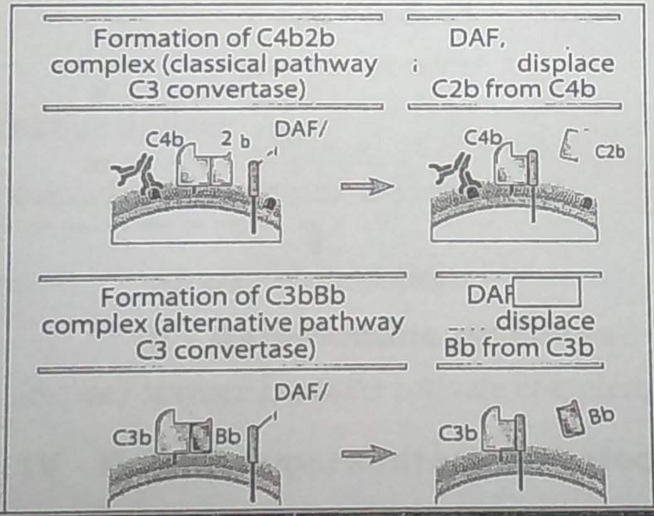
- ↑↑ levels of sialic acid on mammalian cells → *Rapid inactivation of bound C3b* on host cells
- CD59 (Protectin) → ⊖ *C9 polymerization* during formation of MAC

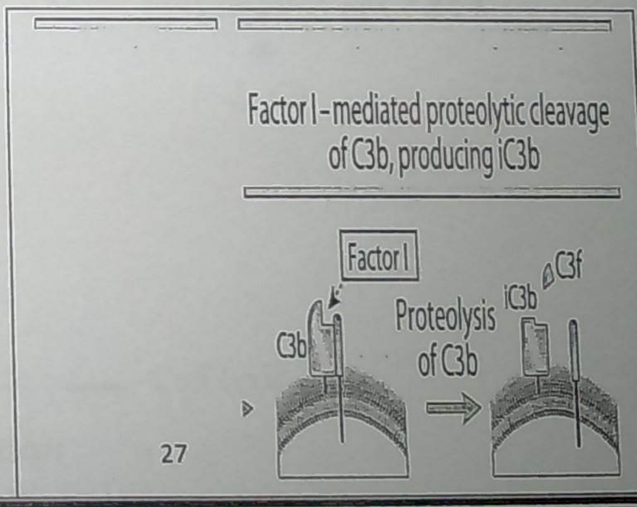


II-Serum proteins → to avoid excess activation of Complements

C1 inhibtor	Decay acceleration factor (DAF)	Factor I	Factor H
Binds C1 → ⊖ *activation of classical pathway*	Displaces C2b from C4b, Bb from C3b → *Dissociation of C3 convertase*	Cleaves C3b → *Inactive C3b (iC3b)*	Cofactor in Factor I action







Clinical aspects of complement

I-Deficiency of complement components

Recurrent acute (pyogenic) bacterial infections

C3 deficiency is the most serious

Loss of biological functions of complement:

i. Lysis by MAC.

ii. Opsonization. → recurrent infection with strept pneumoni

iii. ↑Ab production (⊕ of B cells)

Hypersensitivity

Deficiency of C1, 4 & 2

Defect in complement activation (C3)

Failure to remove ICs from circulation

Deposition of ICs in BVs& tissues

Inflammation & tissue damage

→Type III hypersensitivity & SLE Systimic lobus emtonyus

II-Inherited deficiency of C1 inhibitor (C1 INH)

Heriditary angioneurotic edema

↑ break down (⊕) of C4 &2

(↓ serum free level of C1,2&4) not activated

↑ C3a , 4a & 5a

(anaphylatoxins)

↑ vasoactive amines

↑ capillary permeability & localised edema at mucosal surface

Laryngeal edema — **Airway obstruction**

↑ susceptibility to infections (Latente)

*Chronic **consumption of C2 &C4***

↓ C3

III - Autoimmune diseases

Bound Abs against ***cell surface proteins*** activate complement → Cell lysis

IV - Role in hyperacute graft rejection

Immunogens & Antigens

Immunogenecity

Is the ability of a substance (*Immunogen*) to **induce a specific immune response**

↓

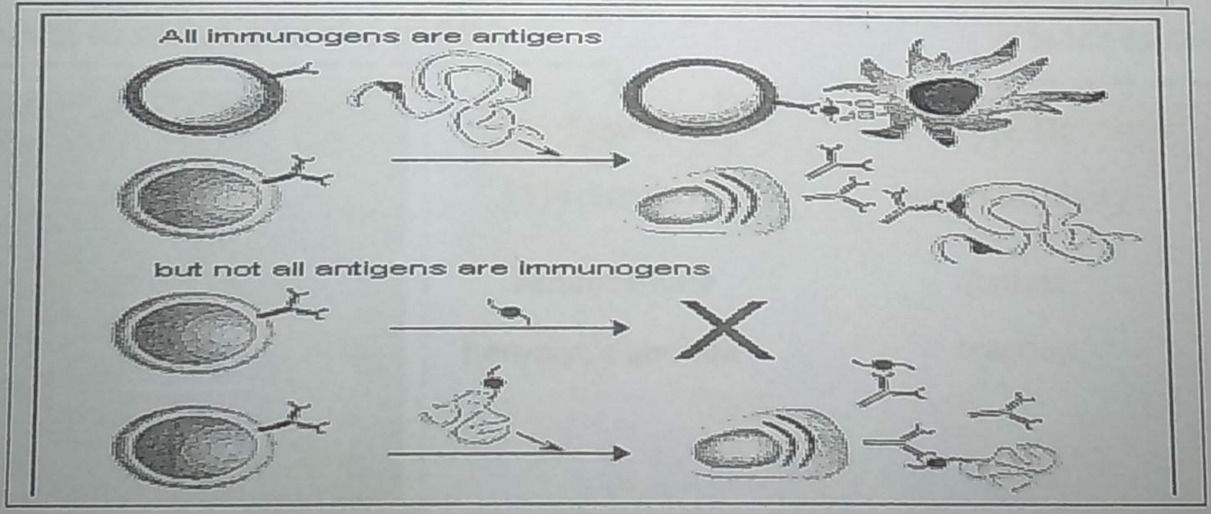
Production of Abs or activated T lymphocytes

Antigenecity

Is the ability of a substance (Ag) to **react (bind) specifically**

with ***final products of IR*** (Abs or activated T lymphocytes)

All Immunogens are Ags,but not all Ags are immunogens

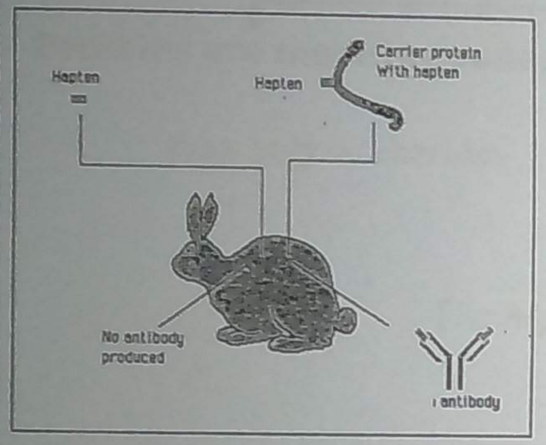


Haptens

A-Characters

Not immunogenic

Due to its **small MW**



Becomes immonogenic

if conjugated to **carrier proteins**

↓

Hapten carrier complex (Immunogen)

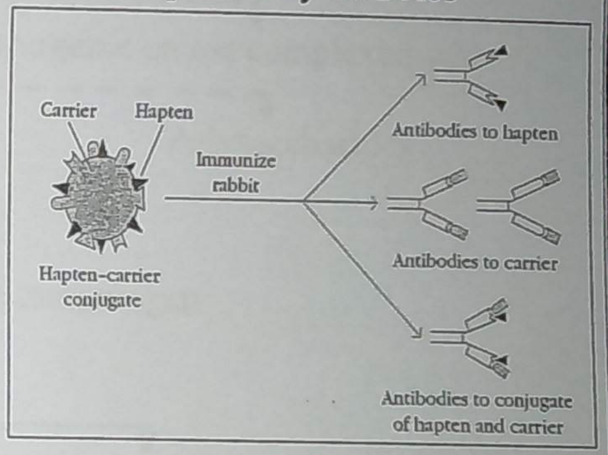
↓

⊕ B cells → Ab production against both

Antigenic

React (bind)

specifically with Abs



B-Examples & medical importance

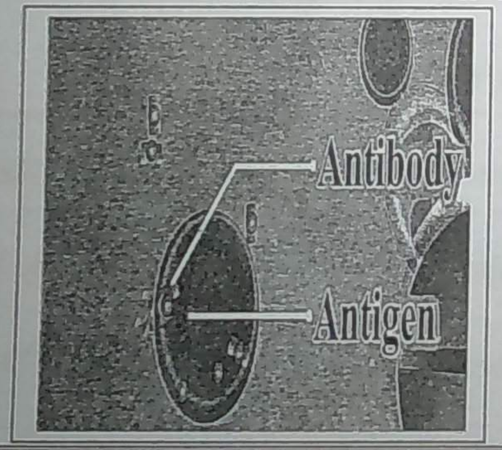
Haptens can induce drug allergy

Penicillin

If binds to serum proteins or RBCs

Type **I** hypersensitivity

Anaphylactic shock



Type **II** hypersensitivity

Autoimmune hemolytic anemia

If binds to skin proteins

Type **III** hypersensitivity

Arthus reaction

Type **IV** hypersensitivity

Contact dermatitis

Factors influencing immunogenicity

1-Foreigness

We are tolerant to self molecules → Only **foreign Ags** are immunogenic

2-Chemical composition

Proteins are more immunogenic than polysaccharides

Lipids & nucleic acids aren't immunogenic unless complexed with

- Proteins
- Polysaccharides

3-Molecular size

The ***higher*** the molecular size → the ***more potent*** the immunogen

4-Dosage

Below a certain dose → ***No*** ⊕ of immunity

Very high dose → ***Immune paralysis***

5-Route of administration

Ags injected **SC , IM & ID** induce the **strongest response**

- Slow rate of absorption → ***(depot effect)***
- ***Carried directly to LNs*** → Processed to ⊕ immune cells

Ags injected **IV** induce **weaker response**

Lack depot effect

Heterophil Ags (cross reactivity)

I-Characters

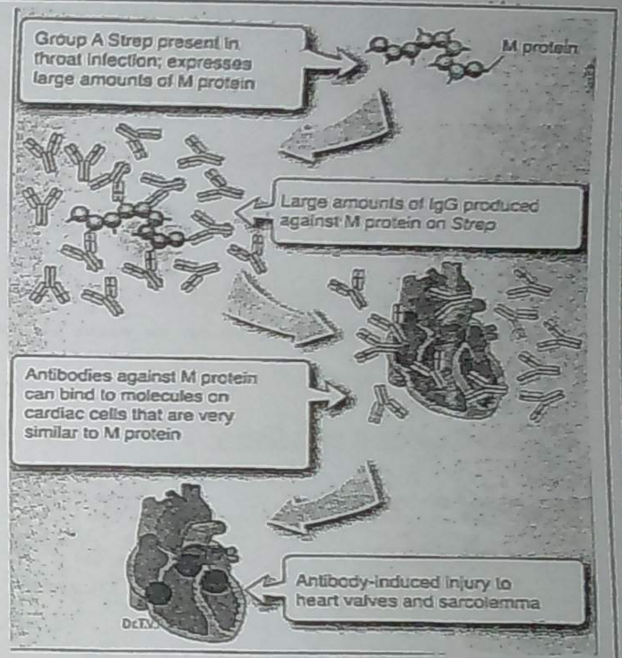
- Derived from **different species:** Organisms,mammals
- *Share one or more epitopes*
- Induce production of **heterophil Abs** → Cross react with **shared epitopes**

Practical Applications

A-Pathogenesis of Rheumatic Fever

Heterophil Abs produced against group A Streptococcus **M protein** → Cross react with ***heart protein myosin***

Rheumatic fever is a classic example of molecular mimicry



B-Laboratory diagnosis

Heterophil Abs in **serum** of patients cross react with **added heterophil Ags** → diagnosis of many diseases

Disease	Causative organism	Used heterophil Ag	Test
1-Syphilis	Treponema pallidum	***Cardiolipin*** (beef heart muscle + cholesterol + lecithin)	Wassermann test
2-Typhus fever	Rickettsia	***Non motile strains of proteus*** (OX19, OX2 & OXK)	Weil Felix test
3-Infectious mononucleosis	Epstein-Barr virus	***Sheep RBCs***	Paul Bunnel test

Monoclonal Abs

Definition

Mc Ab is an Ab produced by

a single clone of B cell

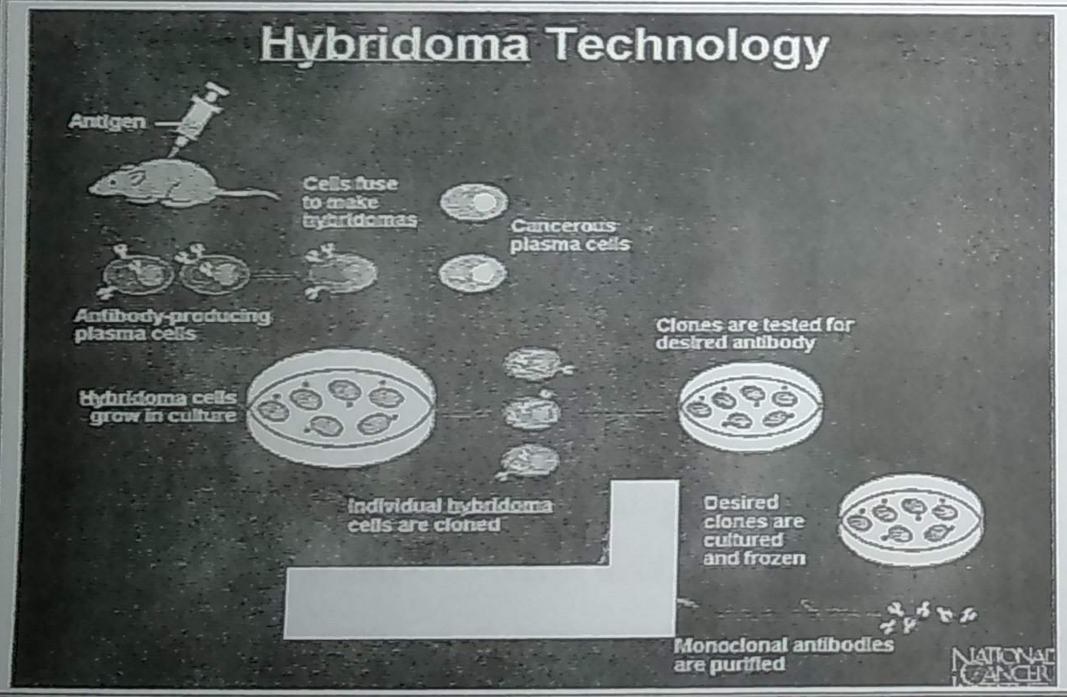
Specific for a single epitope

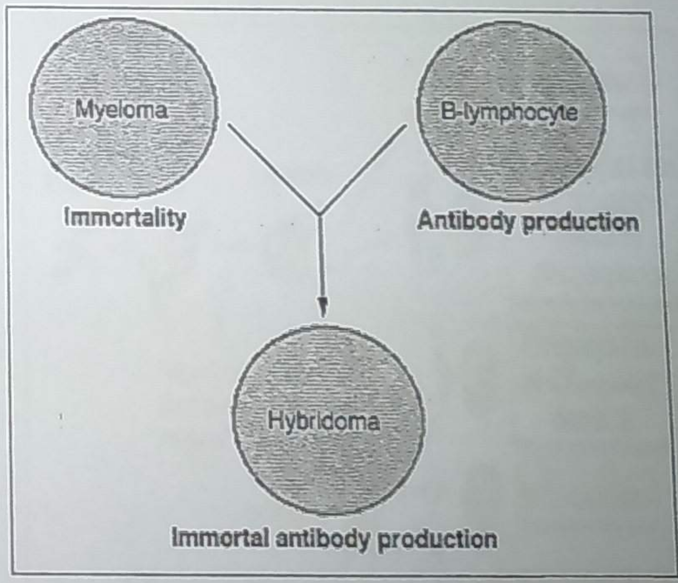
Method of production

B cells producing the **desired single kind Ab** are fused with **tumor cells** (myeloma cells)

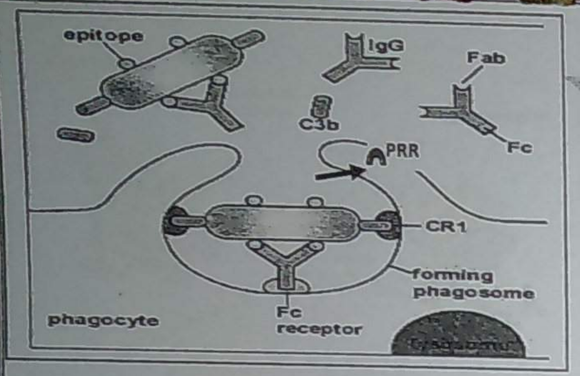
Production of ***hybridoma cells***

- Secrete the desired Mc Ab
- Long lived (indefinite multiplication)





Immunity against microbes



Immunity against EC bacteria

I-Innate immunity

Phagocytosis

Phagocytes bind ECB by

PRRs & opsonin receptors : C3bR & IgGR

Ingested bacteria are killed & digested

by lysosymes

Activated MQ secrete

inflammatory cytokines

Recruitment of leukocytes

to sites of inf.

Complement activation

ECB activate

alternative or lectin pathways

Bacterial ***lysis,opsonization***&

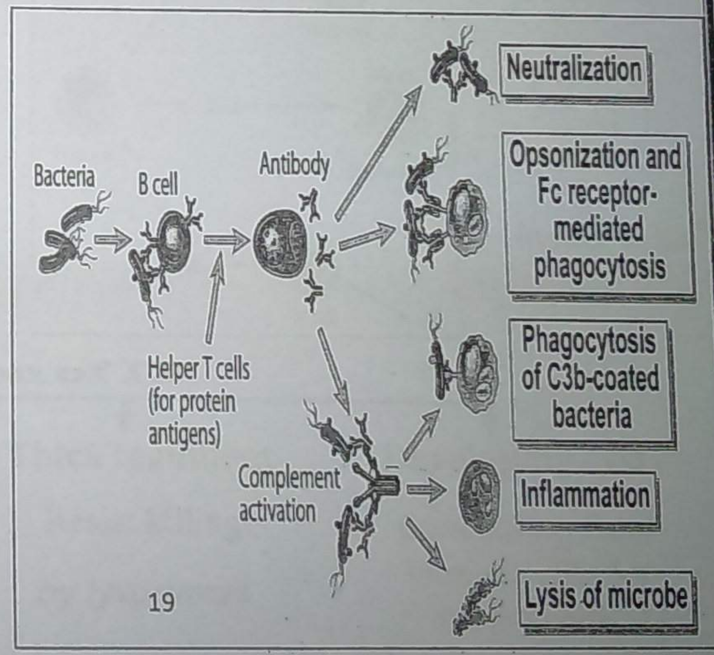
enhancement of ***inflammation***

II-Adaptive immunity

Humoral immunity : the main protective IR

Neutralization **Opsonization** **Complement activation**

By classical pathway



III-Mechanismsof evasion of IR

Antigenic variation of surface Ag

during replication in host

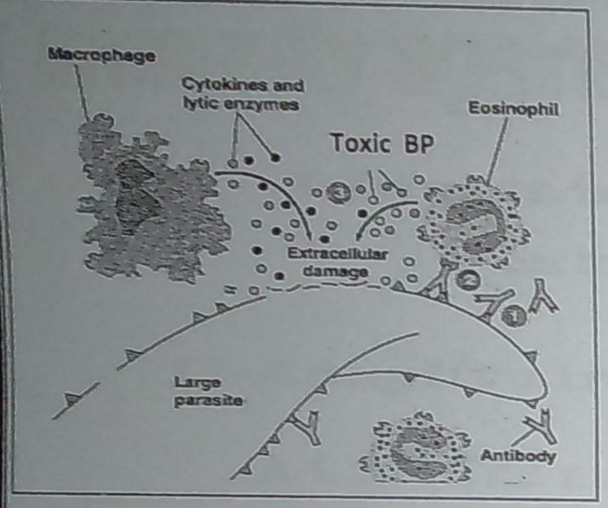
e.g Salmonella &Borrelia

Polysaccharide capsule : antiphagocytic

Sialic acid in capsulated G+ve&-ve bact.

⊖ **complement activation** by alternative path.

Immunity against parasites



I-Innate immunity

Phagocytosis

Although it is the main mechanism, many parasites resist killing

↓

Replicate within MQ

Phagocytes release their granular contents

↓

Kill ***too big parasites to be phagocytosed***

Complement activation

Parasites activate ***alternative*** pathway

II-Adaptive immunity

Humoral immunity : the main protective IR

ADCC

Th2 secrete IL4&5

↓

↑ IgE & ⊕ eosinophils

↓

IgE coating parasites bind to Fcε R on eosinophils

↓

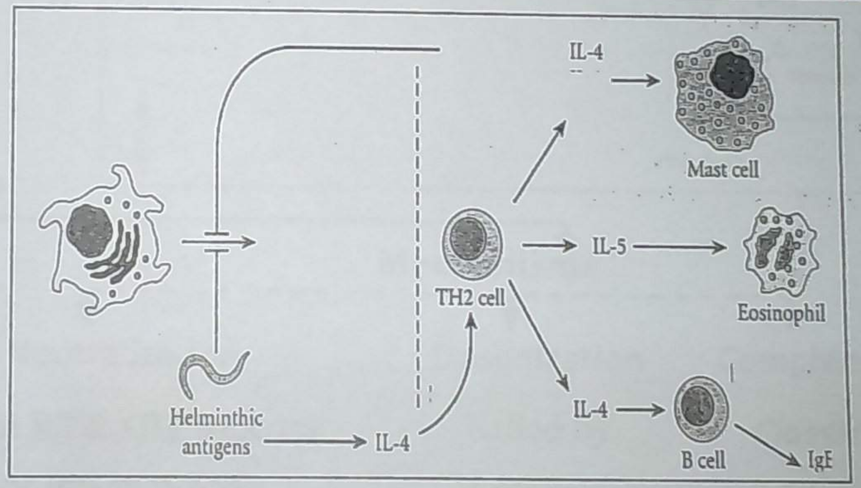
Degranulation

↓

Release of toxic basic protein

↓

Killing parasites by ADCC



CMI

CTLs kill parasites replicating in host cells

III-Mechanisms of evasion of IR

Antigenic variation of surface Ag during replication in host cell

Immunosuppression

⊕ *of T reg*

Production of ***IS cytokines***

Thick tegument

Resist killing ***by lysosymes***

Developing cysts

Concealing from immune effector mechanisms

Immunity against viruses

I-Innate immunity

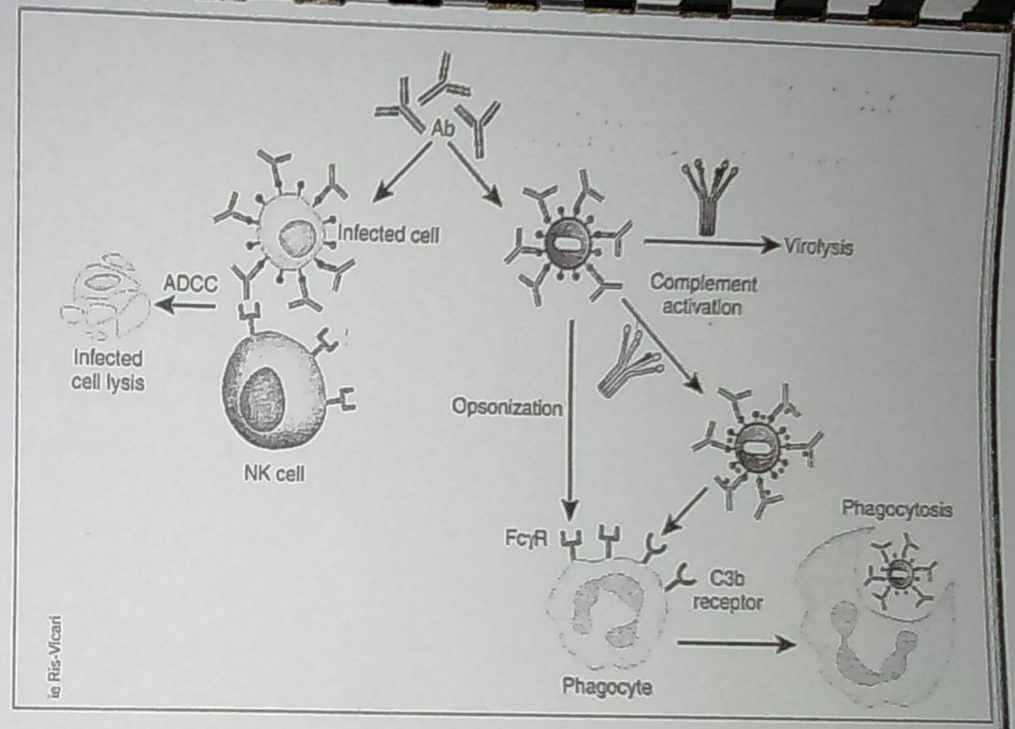
See before

II-Adaptive immunity

A-CMI : The main immunity

See before

B-Humoral immunity



1-Killing viruses

- **Importance**
  - **Before** entering cell
  - **Released** from infected cell
  - **Viremia**
- **Mechanisms**
  - **Neutralization**: ***IgA*** in RT& GIT mucosa or ***IgG*** in blood → ⊖ entry into host cell
  - **Opsonization**: Killed by phagocytes
  - **Complement ⊕**: ***Classical*** pathway

2-Killing VIC

- ADCC through ***NK & phagocytes***
- Complement ⊕